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First Manifestation of IgG4-Related

Highlights

Diagnosis of Intracardiac Infection

Morphological Verification of Tumors

Discovering Thoughts, Inventing Future

VOLUME 24 ISSUE 2 VERSION 1.0

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Significance of the Prevalence of Arterial Bacteremia over Venous Bacteremia in the Etiological Diagnosis of Intracardiac Infection

By Yuriy L. Shevchenko

Abstract- *Background:* The article analyzes the possibilities of increasing the efficiency of cultural bacteriological testing in patients with infective endocarditis by inoculating arterial and venous blood.

Methods: To substantiate the significance of the proposed combination, the experiments were conducted on 18 dogs to study the difference in the bacterial load between the arterial and venous blood. The experiments included standardized blood cultures and injections of the bacterial suspension of S. aureus isolates cultured in agar plates containing 131 I-labeled albumin. In the arterial and venous blood samples, the relative concentration of 131I was determined by recording counts per minute in the well counter chamber. A total of 141 surgical patients with infectious endocarditis (IE) had venous and arterial blood cultures performed to assess the positive test rates compared to the intraoperative results.

Keywords: *infective endocarditis; bacteremia; diagnosis; blood culture.*

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Results: Positive arterial blood cultures were obtained in all experiments, while venous blood cultures were positive in 44.4%. The difference in the bacterial load between the arterial and venous blood samples was 3.81:1. A ganglionic blocker (pentamine 5%, 2.0) was administered to ensure peripheral capillary dilation, resulting in a significant decrease in the difference in arterial bacterial load (2.62:1) due to a reduction in the tissue bacterial filter. Positive arterial blood cultures were reported for 75-94.5% of surgical patients with IE, with the percentage varying by the IE form.

Conclusions: The model and clinical experiments have suggested the concept that arterial bacteremia is more prevalent than venous bacteremia in the context of cardiac localization of IE. The practical application of the suggested concept allows for more reliable confirmation of the cardiac localization of the infection and an increase in the detection rate of microorganisms in the blood.

Keywords: infective endocarditis; bacteremia; diagnosis; blood culture.

I. Introduction

Laboratory diagnosis of bacteremia and imaging results are among the most reliable combinations for the diagnosis of infective endocarditis (IE). However, conventional microbial blood cultures in IE patients are frequently non-diagnostic, with both false positive and false negative tests. These may be caused by a number of confounding factors, such as growth difficulties, sampling issues, suspected pathogen characteristics, or inadequate preculture treatment strategies (early and inappropriate antimicrobial treatment). Given the same factors, it is also advisable to exercise caution when interpreting positive tests.[1-5]

Venous blood culture represents the most common diagnostic tool currently available for the detection of bacteremia. However, the diagnostic reliability of blood cultures may potentially be constrained despite the unambiguous clinical presentation of generalized infection and sepsis. To overcome this limitation, the Russian and international clinical guidelines recommend collecting at least three blood samples (or preferably to obtain three positive identical blood cultures). Nevertheless, a considerable proportion of conventional blood cultures (16–80%) remain inconclusive, with both false negative and false positive results.[1,6,7] The difficulty in culturing certain microorganisms and the challenges in interpreting the results obtained are the two main reasons for this.[6,8] The advances in alternative diagnostic approaches, such as polymerase chain reaction (PCR) and sequencing, have not significantly altered the landscape of etiological diagnosis for IE. The ambiguity of the results[6,9-12] has reserved these diagnostic tools as supplementary options in both Russian and international clinical guidelines.[1,13]

Efforts to increase the probability of true positive blood cultures based on the infectious biology, etiology, and pathogenesis of IE have encouraged the authors of this paper to initiate both *venous* (as is generally accepted) and *arterial blood sampling for microbiology.* This was based on the assumption that the left heart (aortic and/or mitral valves, less often left atrial or left ventricular mural vegetations) is the most frequent location of IE. From these sites, bacteria are occasionally released into the arteries of the systemic circulation. The subsequent mechanical and biological blood filtration occurs through tissue ultracapillaries. This results in the blood passing into the venules and veins with only minimal microbial contamination.[2,6,14]

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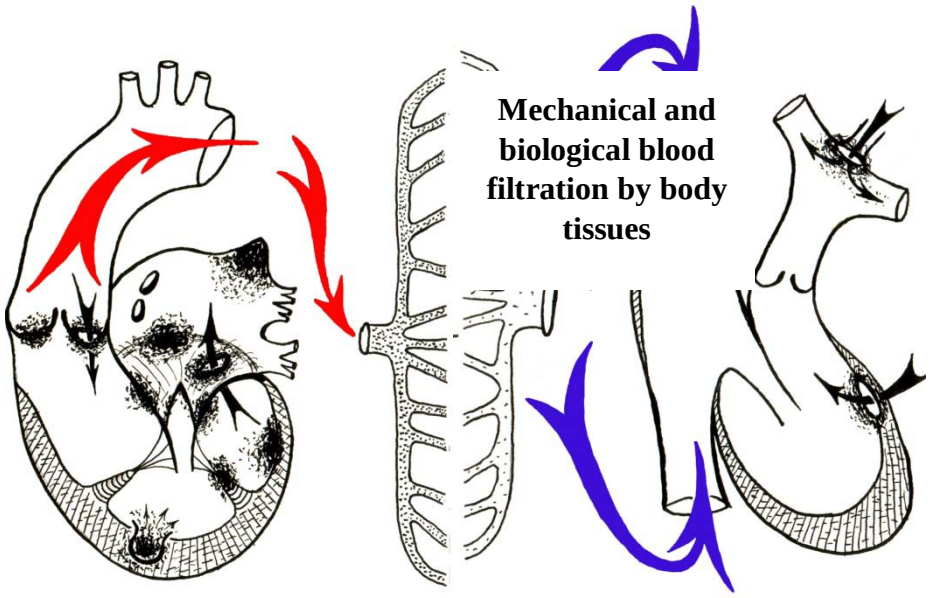

Figure 1: Schematics of the blood purification mechanism that elucidates the difference between arterial (Ba) and venous (Bv) bacteremia

It can be reasonably assumed that the bacterial load for arterial bacteremia is higher than for venous bacteremia. The arterial blood samples are thereby more likely to display higher positive detection rates than venous blood samples (Fig. 1).

II. Methods

The patients have given their informed consent for participation in the research study. The study was approved by the institutional research ethics committee and specifying the guidelines for care of animals that have been followed.

A dedicated experimental study was conducted to substantiate the hypothesis that IE is associated with a higher bacterial load in arterial blood than in venous blood (Fig. 2).

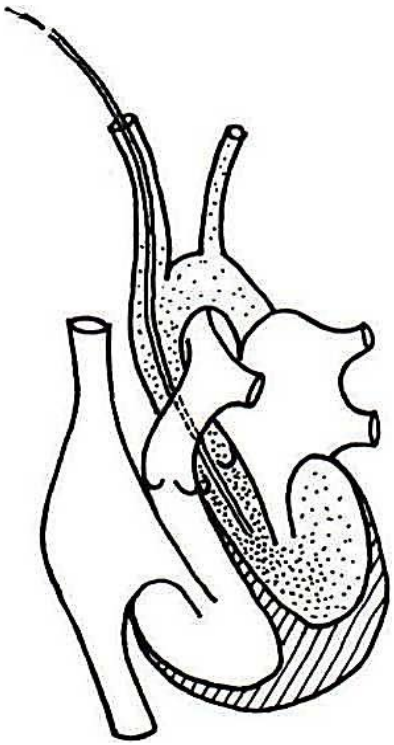

Figure 2: Schematics of experimental bacterial elimination from the LV into the arterial circulation

The qualitative assessment of the differences in bacterial loads between arterial and venous blood was performed in 18 dogs. A bacterial suspension was injected via a catheter into the left ventricle (LV) through the carotid artery in animals under thiopental anesthesia. Blood samples were collected from the femoral artery, and 12–15 seconds later, blood was drawn from the right atrium (RA) via a catheter inserted through the jugular vein. This model simulated transient bacteremia localized to the left heart, which is the most common site of IE. A volume of 50 mL of broth medium was inoculated with 5 mL of blood (Fig. 3).

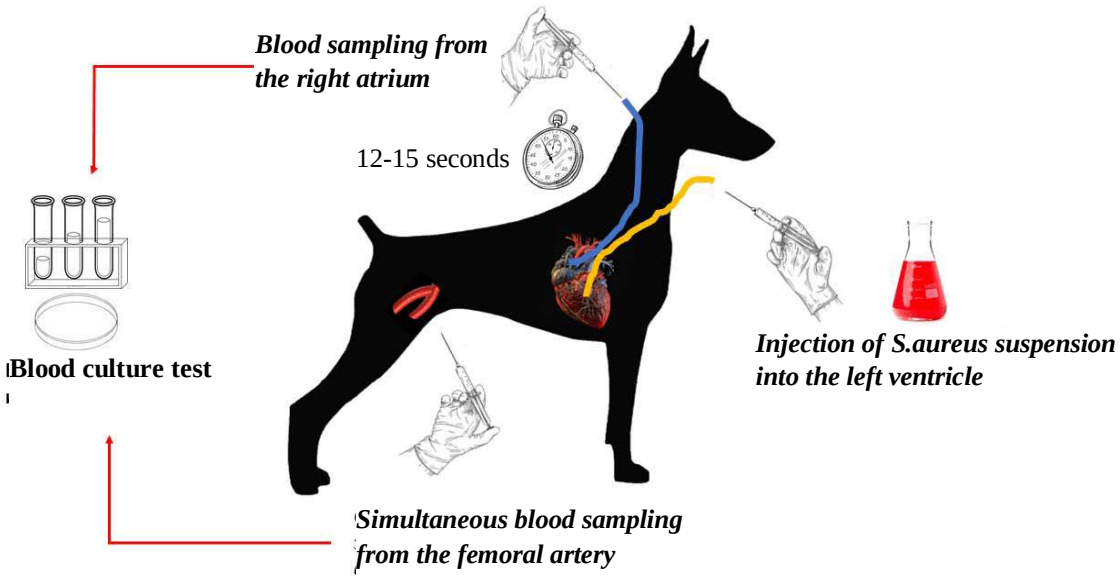

Figure 3: Graphical presentation of the first series of experiments (refer to the test for further clarification)

The second series of experiments was designed to measure the differences in the bacterial load between arterial and venous blood samples using the radionuclide method. The bacterial suspension of *S. aureus* isolates cultured in agar plates containing ^{131}I-labeled albumin was injected into the LVs of experimental animals. The arterial and venous blood samples were analyzed to determine the relative concentration of ^{131}I (counts per minute in 1 mL of blood) in the well counter chamber (Fig. 4).

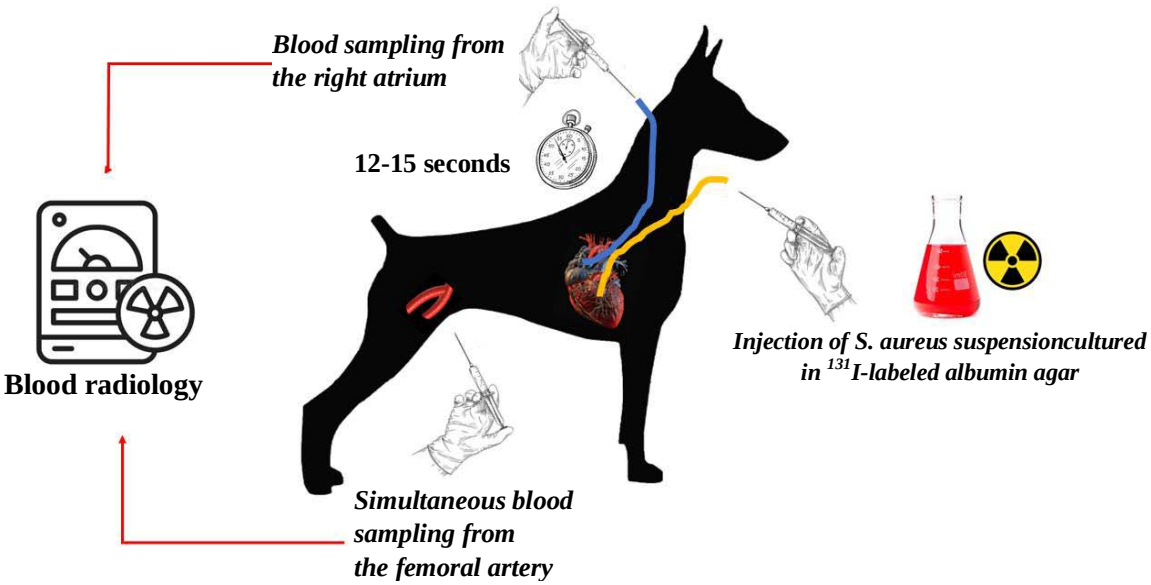

Figure 4: Graphical presentation of the second series of experiments (refer to the test for further clarification)

A comparable series of experiments was conducted to ascertain the contribution of the mechanical component in the overall blood filtration by tissues following the administration of ganglionic

blockers (pentamine 5% 2.0). This resulted in peripheral capillary dilation, which was assumed to increase the penetration of bacterial conglomerates into the venous vessels, thereby reducing the difference in the bacterial load between the arterial and venous blood (Fig. 5).

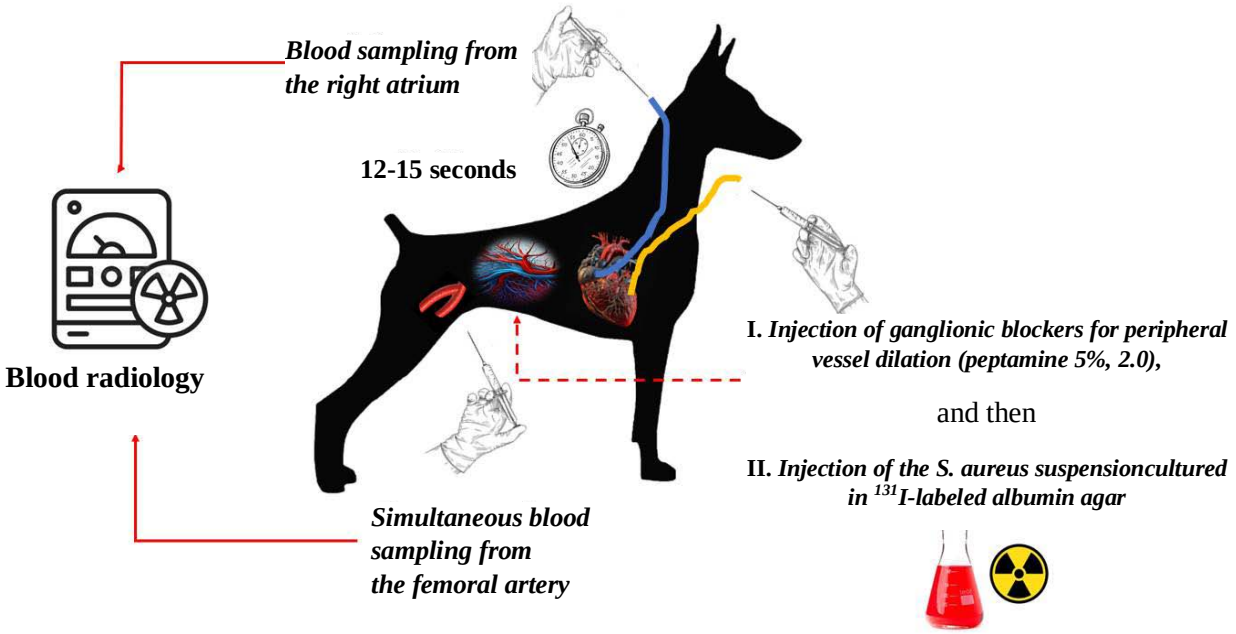

Figure 5: Graphical presentation of the third series of experiments (refer to the test for further clarification)

The fourth series of experiments attempted to evaluate the filtration capacity of the pulmonary circulation, as well as the difference in the blood load for arterial and venous bacteremia localized in the right heart. For this purpose, an isotopic bacterial suspension was injected into the peripheral vein of the animal's forelimb. Four or five seconds later, the first blood sample was drawn directly from the right ventricle through a catheter inserted through the jugular vein to measure an initial concentration. After 6–8 seconds of blood sampling from the right ventricle, the blood sample was obtained from the femoral artery. Following an interval of 12–15 seconds, venous blood samples were collected from the right ventricle (Fig. 6).

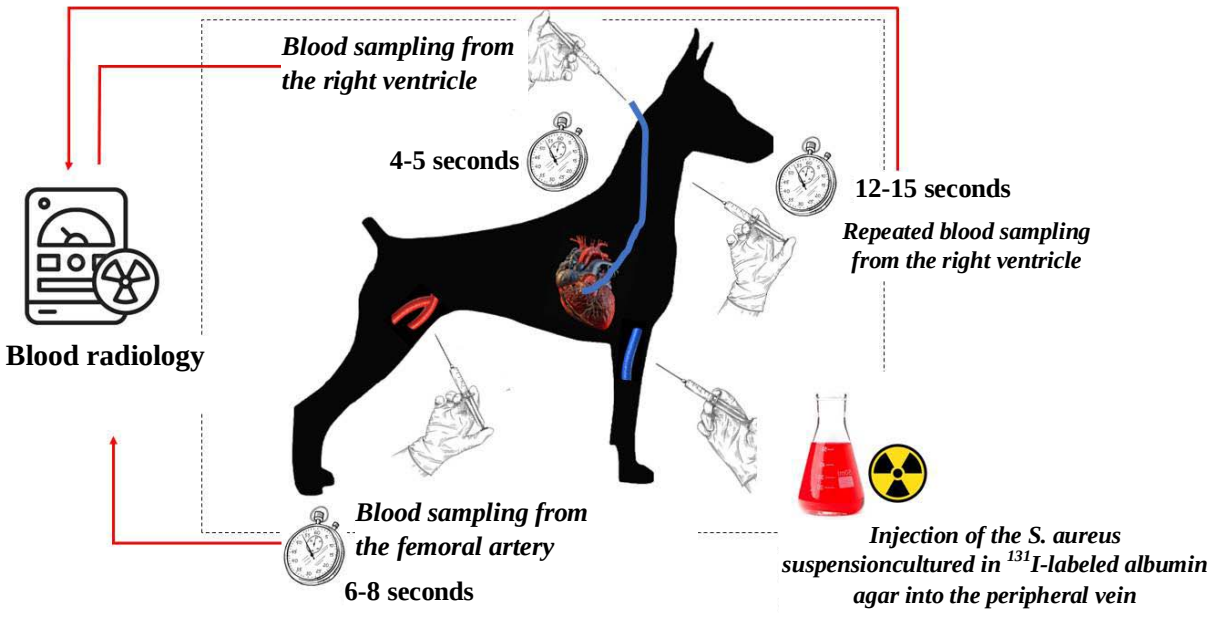

Figure 6: Graphical presentation of the fourth series of experiments (refer to the test for further clarification)

To further substantiate the proposed hypothesis, the authors conducted examinations on 141 patients presenting with signs of intracardiac infection.

Arterial and venous blood samples were obtained from all surgical patients for blood culture testing. Blood samples were collected in accordance with standard blood culture collection practices, with an amount of 10 mL of blood per 100 mL of the suitable medium. Venous blood was collected via puncture of the ulnar vein or through a catheter inserted into the subclavian or superior vena cava. Arterial blood was drawn from the femoral artery via puncture, in accordance with the established standard procedure.

Prior to blood collection, patients were instructed to perform physical exercises of moderate intensity to enhance the mechanical effect on the contaminated heart valves, thereby facilitating a more substantial elimination of bacteria into the bloodstream. An increase in the functional load on the heart was achieved by changing from a lying to a sitting position five to seven times. It is noteworthy, however, that the physical exertion was not suitable for hyperthermic or tachycardic patients or those whose condition was considered severe.

III. Research Evidence

All 18 arterial blood samples and only eight venous blood samples (44.4%) were positive for microbial contamination in first experimental series. The results of second series of experiments are presented in Table I.

The calculated load difference in the arterial blood was 3.81:1. The bacterial load in the arterial blood is crucial for the development of IE localized in the left heart.

Table I: Radionuclide measurements of simulated arterial and venous bacteremia localized in the left heart

Number of experiments	Counts per minute (M + t)		
	Reference value	Arterial blood	Venous blood
10	2650±54.5	1764.3±43.5 P<0.05	462.5±14.4 0.03 P<0.05

The study results with ganglionic blockers shown in Table II demonstrate the significantly decreased difference in the bacterial load between the arterial and venous blood.

Table II: Effect of ganglionic blockers on the difference in the bacterial load between the arterial and venous blood

Number of experiments	Counts per minute (M + m)		
	Reference value	Arterial blood	Venous blood
10	2724±49.6	1638.9±34.5 P<0.05	789.4±19.9 P<0.05

The results of this series of experiments are presented in Table III.

The evaluation of the filtration capacity of the pulmonary circulation and the difference in the bacterial load for arterial and venous bacteremia localized in the right heart demonstrated a value of 2.62:1, which is responsible for the development of IE.

Table III: Measurements of the blood load for arterial and venous bacteremia localized in the right heart

Number of experiments	Counts per minute (M + t)			
	Reference value	Blood flow from the right ventricle	Arterial blood	Blood flow from the right ventricle
10	2840±55.4	1984.5±21.6	1015±16.2 P=0.05	386.5±9.19 P<0.05

Experimental studies have demonstrated that the bacterial load in arterial blood is significantly higher than in venous blood for the cardiac localization of infection. The experimental model of severe transient bacteremia localized in the left heart demonstrated that microbial detection rates were higher for arterial blood (100%) compared to venous blood (44.4%). A quantitative assessment of the bacterial load in arterial and venous bacteremia simulated using ^{131}I-labeled microorganisms demonstrated that the bacterial load in the arterial blood was approximately 4.5–5 times higher than in the venous blood. Furthermore, the series of experiments conducted with the administration of a ganglionic blocker demonstrated the significance of

direct mechanical blood filtration by tissues. The direct effect of the ganglionic blocker on filtration capacity (arteriole dilation and the opening of arterio-venous anastomoses) contributes to the easier penetration of bacterial conglomerates into the venules and veins. Consequently, the difference in the bacterial load between the arterial and venous blood is significantly decreased. The findings of the experimental study suggest that while the pulmonary circulation displays a considerable degree of filtration capacity, there is a higher bacterial load associated with arterial bacteremia than with venous bacteremia, even in the presence of a septic focus in the right heart.

Bacteriological Diagnosis of IE in Clinical Practice: The preoperative blood culture tests for each patient consisted of three to seven arterial and venous blood samples. A total of eight to ten blood samples were collected during the postoperative period. Bacterial cultures were identified in the blood, surgical specimens, such as excised valves, papillary muscles, vegetations (infected thrombotic masses), and tissue specimens (subcutaneous fat, muscles), i.e., so-called filtration material, from the surgical wound.

A total of 120 patients had between three and six positive arterial blood cultures prior to surgery. The microbial strains present in the surgical specimens of these patients were identified. A total of 45 patients exhibited single positive results in their venous blood cultures.

The pathogens were identified in 141 patients. The pathogens were detected in the arterial blood of 120 individuals, including 45 patients who had positive venous blood cultures. In 21 individuals with persistent negative arterial and venous blood cultures, the pathogens were isolated from surgical specimens. The patients were admitted to the hospital between three and five months after the onset of the disease. Prior to admission, they had received aggressive antibacterial therapy. Their recovery process was generally uncomplicated, with no symptoms of sepsis. However, they presented with significant valve changes, circulatory failure, and various complications in internal organs. Histopathology of heart valves in all patients demonstrated bacterial invasion in deep layers of detritus or calcium conglomerate covered with massive organized blood clots or a solid fibrin layer. It was unlikely that microorganisms could pass into the blood flow from this site. Fifteen patients had achieved remission prior to the surgery, so the growth of microorganisms was not detected either in the blood or in the heart valves.

Five patients who presented with a typical clinical picture of IEand respective surgical findings also had sterile blood and heart tissue cultures. However, the histological examination of the affected tissues revealed the presence of a considerable round-cell infiltration of histiocytes in the damaged and scarred valves. This indicates the occurrence of a long-term, chronic inflammatory process, which was most likely of an infectious origin.

The subsequent years of experience in the treatment of intracardiac infections have definitively demonstrated the *prevalence of arterial bacteremia over venous blood load.* The results of blood and surgical specimen culture tests for patients exhibiting varying degrees of clinical symptoms are presented in Table IV. Consequently, the blood culture values reported for IE patients, as compared to intracardiac microbiological findings indicate a high diagnostic significance of *arterial* blood cultures.

Table IV: Blood and surgical specimen culture tests in IE patients with various clinical symptoms

Clinical symptom severity	Pre-operative positive blood cultures		Bacteria detection in heart specimen (surgical specimen)
	Venous blood	Arterial blood	
IE with full-scale clinical picture	40%	94.5%	95%
IE with no significant clinical symptoms	15%	75%	98%
Asymptomatic IE	—	—	25%

IV. Discussion

The identification of pathogens in the context of targeted antimicrobial therapy is of great significance, as it directly influences the treatment plan, particularly for cardiac surgical patients with purulent septic infections.[2,15,16] The IE epidemiology has proven to be highly variable over the past decades. On the one hand, the spectrum of identified IE pathogens is continuously expanding, and their ratio in different cohorts of patients is determined by both patient characteristics (age, underlying and concomitant diseases)[17] and medical care facility experience (cardiac surgery, arrhythmia and electrophysiology, nephrology). On the other hand, the false negative rates of blood culture tests tend to increase with the prevalence of fastidious, aggressive multidrug-resistant pathogens.[1,6,8,12]

The diagnostic significance of bacterial blood cultures varies significantly, ranging from 20 to 65% or more.[1,8,18,19] This may be attributed to the early and aggressive antibacterial therapy, pathogen character-

ristics (including rare hard-to-cultivate microorganisms, fungi, and intracellular bacteria), and limited options for microbiology testing methods.[13]

In practice, a positive blood culture may be obtained from only 45–50% of hospitalized patients with acute IE and from 15–25% with subacute or indolent IE. This is contingent upon the microbiological laboratory having the requisite experience and facilities.[1,6,13,14,20] Furthermore, the pathogen is most likely to be isolated - from the patient's blood at the clinically advanced stage of the disease, when the infectious process has generalized and gross morphological changes appear in internal organs (heart disease, diffuse glomerulonephritis, embolism, septic meningitis, etc.).

The IE diagnosis is still based on a comprehensive assessment of the patient, which includes an analysis of the medical history and clinical data. The Duke criteria may be of substantial utility in standardizing approaches to the detection of intracardiac infection and integrating the entire process of IE verification into a single program. However, these criteria are hardly utilized in practice. Their use is primarily limited to IE specialists or in the retrospective setting, where there is sufficient information available to make an accurate diagnosis. This also causes a low frequency of using bacteriological testing in patients with suspected IE. It is also an important reason for increasing the diagnostic significance of bacteriological diagnosis.[2,3,18]

At present, the range of microbial studies includes imaging (bacterioscopy) and culture-based methods and +/- mass spectrometry, molecular biological (MALDI-TOF MS, PCR, FISH), and serum immunochemistry (antinuclear antibodies, anti-phospholipid antibodies, anti-porcine protein antibodies, anti-xenogeneic antibody, etc.). In the event that the surgical procedure involves the site of an intracardiac infection, it is essential to consider histological findings using standard (Gram) and specific staining techniques.[2,18,21]

Microbiological (culture-based) blood testing offers a number of significant advantages. These include high sensitivity (a detection rate of 10^2 mc/mL or more), high specificity, the ability to determine antibiotic sensitivity and antibiotic resistance, and relatively low cost. Among the limitations are the significant influence of the media and inoculation conditions, the lengthy duration of the procedure (up to 120 hours or more), the stringent requirements for biological sample collection, and the high false negative rates.[18]

The use of blood PCR has been demonstrated to be highly effective in patients with negative blood cultures, particularly in the early stages of the etiological diagnosis of IE. Kotova et al. demonstrated that the use of PCR diagnostic testing resulted in a significantly higher probability of lifetime pathogen identification in the blood, 76.6%.[13,18]

Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) is being incorporated into current diagnostic approaches, enabling the identification of unique protein spectra associated with the pathogen. The substance of this method is the accurate identification of microorganisms based on the analysis of their protein spectra. MALDI-TOF MS offers a number of advantages, including high analytical specificity and sensitivity, the ability to identify more than 2,700 microbial species from the most up-to-date reference database, and low operating costs. The method's inherent limitations diminish its diagnostic value. The following limitations have been identified, i.e., potential spectral interference, inability to differentiate similar or closely related organisms (e.g., *Escherichia coli* and *Shigella* spp., various fungi), and significant limitations related to the identification of polymicrobial flora (no more than two microorganisms) and the determination of antibiotic sensitivity and antibiotic resistance. Obtaining positive blood cultures (either primary or those grown on solid media) represents a crucial initial step in the diagnostic process.[7,18]

Although novel microbial detection techniques have been implemented, blood culture testing remains the primary method for pathogen identification. The results of experimental and clinical studies have demonstrated a higher detection rate in arterial blood samples compared to venous blood samples. The obtained clinical data suggest that the diagnostic value of the arterial blood culture testing is significantly higher than that of similar venous blood cultures. The difference in the bacterial load between the arterial and venous blood is likely to be associated with the biological and mechanical blood filtration through body tissues. Moreover, the quality of microorganisms that have passed through a tissue filter and entered the venules and veins of the systemic circulation may change to a certain extent. The probability of their proper growth in artificial media thereby decreases.[2,6,14]

It should be noted that more significant arterial bacteremia can also occur in suppurative lung diseases, since the runoff blood collects in the left heart. The oxygenized, contaminated blood flows from the left heart into the arteries of the systemic circulation. Nevertheless, the clinical and instrumental modalities for the recognition of suppurative lung diseases are numerous, even in the absence of blood culture testing. Nevertheless, the difference (or no difference) in the bacterial load between the arterial and venous blood (or no difference) both in IE and suppurative lung diseases may be considered a criterion of the qualitative assessment of a macroorganism, including general biological reserves, body defenses, immunity, etc. In this context, the concurrent culture-based testing of venous and arterial blood is becoming increasingly important.

V. Conclusion

It can be demonstrated that the phenomenon of the *prevalence of arterial bacteremia over venous bacteremia* with an infection focus localized in the heart is based on the microcirculatory tissue filtration of bacteria. This has a very important theoretical and practical significance. This phenomenon specifies the infection localization, significantly improves the pathogen detection rate and identification of its pathogenic properties, and enhances sensitivity to antibiotics. This may result in the development of the most efficient individual program of conservative and surgical strategy and significantly improve the treatment outcomes for this life-threatening disease.

Declaration

Local Ethics Committee of the Pirogov National Medical and Surgical Center of the Russian Ministry of Health; Stukolova TI; No.2; February 15, 2022.

Conflicts of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Papulonodular Lesions in Photo Exposed Areas as First Manifestation of IgG4-Related Disease

By Araújo FM, Paula CDR, Veridiano F. A., Takano G. H. S. & Costa I. M. C

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A 53-year-old woman described a 15-year history of erythematous and pruritic papulo-nodular lesions, mostly in photoexposed areas of the face, neck and upper limbs. She explained that the lesions evolved with ulceration, healing and residual dyschromia. Furthermore, she reported relapsing lymphadenomegaly 2 years ago, primarily in the cervical, axillary and inguinal chains.

Keywords: igG4-related disease; dermatology.

GJMR-F Classification: LCC: RC280.S5, RC280.L8

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Abstract- IgG4-related disease (IgG4-RD) or IgG4 syndrome is a chronic inflammatory condition of presumed autoimmune etiology, affecting mainly men in their sixth decade of life. It has a good prognosis following instituted treatment and is characterized by infiltration of IgG4 + plasma cells, predominantly in the pancreas, bile duct, lymph nodes, kidneys, retroperitoneum, lungs and salivary, parotid, submandibular and lacrimal glands. Skin manifestations of IgG4 syndrome are uncommon but should be known to the dermatologist. This report details a rare case of IgG4 syndrome involving cutaneous and lymph nodes.

A 53-year-old woman described a 15-year history of erythematous and pruritic papulo-nodular lesions, mostly in photoexposed areas of the face, neck and upper limbs. She explained that the lesions evolved with ulceration, healing and residual dyschromia. Furthermore, she reported relapsing lymphadenomegaly 2 years ago, primarily in the cervical, axillary and inguinal chains.

On examination, erythematous papulonodular lesions were observed in the frontal, temporal, malar, cervical and upper limb regions. Additionally, there were palpable, mobile and fibroelastic lymph nodes of 1-4cm, some of which were confluent and forming a mass effect, present in the right axillary, left axillary, cervical and inguinal chains, bilaterally.

A lymph node biopsy showed reactionary lymphadenopathy, without evidence of neoplasia. The skin biopsy revealed an epidermis with pseudoepitheliomatous hyperplasia and dermal inflammatory infiltrate, consisting mainly of lymphocytes, plasmocytes and histiocytes.

The immunohistochemistry of the cutaneous lesion was positive for CD138 plasmacyte antigen, with over 30 IgG4 + plasma cells/high power field. Other complementary exams showed: total IgG 2130 mg/dL, IgG4 562mg/dL.

Thus, the diagnosis made was IgG4-related disease. Prednisone was started at a dose of 40mg/day, resulting in improvement in the lymph nodes and skin lesions.

Skin is rarely involved in IgG4 syndrome. Previous studies identified skin lesions in 4.2% of 118 Chinese patients and in 6.3% of 80 Japanese patients, respectively. These lesions present as nodules, papules or plaques that may be pruritic, preferentially affecting the head and neck, and less commonly, the trunk and extremities. Differential diagnoses include nodular prurigo, rosacea, angiolymphoid hyperplasia with eosinophilia, xanthogranulomas and cutaneous lymphomas.

Lymphadenopathy is often present in IgG4 syndrome and may manifest in only one chain or be generalized. Cutaneous involvement is strongly associated with lymph nodes (in 46% of cases), as was the case in this patient.

One diagnostic model proposed encompasses 3 pillars: 1) clinical criterion characterized by swelling or mass affecting one or more organs; 2) serum IgG4 levels > 135mg/dl; 3) histological criterion with lymphoplasmacytic infiltrate and fibrosis, along with a percentage of IgG4+ plasma cells/IgG+ plasma cells >40% and over 10 IgG4 + plasma cells/high power field. The presence of the three criteria confirms the diagnosis, the satisfaction of criteria 1 and 3 makes the case probable, while the fulfillment of criteria 1 and 2 indicates a possible case. Our patient met all 3 criteria, leading to a definitive diagnosis of IgG4 related disease.

Systemic corticosteroids are the first line of therapy, administered at a dose equivalent to 0.6mg/kg/day of prednisone in remission, and at lower doses for maintenance. Alternatives to corticosteroids include azathioprine, methotrexate and mycophenolate. Recently, Rituximab (anti-CD20) was associated with reduced disease activity.

This instance of IgG4 syndrome manifested clinically in a female, with cutaneous and lymph node involvement. We emphasize that, faced with papulonodular lesions and large masses of adenomegaly, skin biopsy can be a valuable and accessible tool to diagnose IgG4 syndrome, ruling out neoplasms, avoiding inappropriate management and late diagnosis.

Keywords: igG4-related disease; dermatology.

I. Case Report

a) Introduction

IgG4-related disease (IgG4-RD), also called IgG4 syndrome or IgG4-associated disease, is a chronic inflammatory condition of presumed autoimmune etiology. It is characterized by the potential for IgG4+ plasma cell infiltration in various tissues and can affect many organs, although the incidence and prevalence have not been established1. Classically, it is described in men — 3 to 4 men for every woman — on average in the sixth decade of life, although rare cases have been identified in other age groups, including children.[2,3]

The disease was first described in the pancreas and was called lymphoplasmacytic pancreatic sclerosis4. In addition to the pancreas, other sites have common involvement such as lymph nodes, bile duct, salivary gland, parotid gland, submandibular gland, lacrimal gland, kidney, retroperitoneum and lung.[1,5]

The prognosis of patients with IgG4-related disease tends to be good after treatment, with mortality being an unexpected event. Complications and

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functional organ failure due to fibrosis are related to delays in diagnosing the disease.

This disease has been better understood in recent years and, as a potential cause of morbidity, it must be known by the doctor so that there is clinical suspicion, correct diagnosis and appropriate management. In this context, the aim of this paper is to report a case of IgG4-associated disease with cutaneous and lymph node involvement, and to discuss it on the basis of the literature.

b) Clinical Case

A 53-year-old female patient came for medical assessment complaining of severe pain, difficulty mobilizing her right upper limb and lymphadenomegaly in the right axillary region with phlogistic signs for 10 days. Associated with her current condition, she reported an unmeasured fever, hyporexia and a loss of approximately 4 kg over the period.

He said that in the last two years he had seen a sudden increase in several lymph nodes, mainly in the cervical, axillary and inguinal chains, which had regressed after taking antibiotics and corticosteroids. However, she said that the current condition was the most intense she had experienced so far.

He also reported skin lesions mainly on the face, trunk, and upper limbs for 15 years. He reported that the lesions were erythematous, papulo-nodular and pruritic, which often evolved with ulceration, scarring, and residual dyschromia. Previous biopsies of the skin lesions suggested a diagnosis of rosacea, polymorphous eruption in the light and nodular prurigo. Noteworthy, in her history, she reported treatment for American Tegumentary Leishmaniasis with skin involvement 2 years ago and reported having systemic arterial hypertension.

Physical examination in the right axillary region revealed multiple enlarged and confluent lymph nodes, forming a mass of approximately 5 cm in its largest diameter. Presence of associated heat, redness, and edema. Impression of mobile and fibroelastic lymph nodes varying in size from approximately 1 to 3 cm without associated phlogistic signs, palpable in the left axillary, cervical and inguinal regions bilaterally. In addition, erythematous papulo-nodular lesions were present mainly on the face and neck, and to a lesser extent on the neck, trunk and limbs, the latter also showing a marked presence of residual dyschromia.

The patient underwent tests for diagnostic investigation, considering the hypotheses of lympho-proliferative neoplasia, ganglionic tuberculosis, histoplasmosis and paracoccidioidomycosis.

Computed tomography of the chest showed the presence of confluent lymphadenomegaly in the right axillary chain, forming a mass with a center of necrotic, measuring approximately 56 x 40 mm in their largest diameters. Other non-confluent lymph nodes of increased size were observed in the ipsilateral axillary chain, left axillary chain and retroperitoneum. Abdominal CT scans showed prominent lymph nodes in the common iliac chain and bilateral inguinal nodes.

The following were negative: blood culture; culture for mycobacteria and fungi in lymph node aspirates; serology for paracoccidioidomycosis, histoplasmosis and coinfections; non-reactive PPD.

The skin biopsy of the right axillary region showed epidermis with pseudoepitheliomatous acanthosis, a dense inflammatory infiltrate made up of lymphocytes, plasma cells and histiocytes, permeated by some neutrophils and rare osinophils in the dermis. No parasites were found in the skin fragment evaluated. An excisional biopsy of the right inguinal lymph node showed reactive lymphadenopathy with a pattern of follicular and paracortical hyperplasia, with no evidence of neoplasia.

Other complementary tests were requested, including total IgG 2130 mg/dL; IgG4 562 mg/dL; rheumatoid factor 28.8 UI/ml; and C4: 5.75 mg/dl; FAN 1:640 homogeneous pattern; anti Sm negative; anti-Dna negative; anti-SSA negative; anti SSb: negative.

Based on the patient's history of recurrent lymphadenomegaly, t h e presence of papulo-nodular lesions with a chronic course, a skin biopsy with lymphoplasmocytic infiltrate and an increase in IgG4, the hypothesis of a disease was put forward related to IgG4. Immunohistochemistry of the previous biopsy taken from the right axillary region was requested. The immunohistochemistry was positive for CD138, a plasma cell antigen. There were more than 30 IgG4 cells per high magnification field, which corroborated the diagnosis of IgG4-related disease with lymph node and skin involvement.

In this context, to induce remission, the decision was made to introduce corticosteroids at a dose of 40 mg/day of prednisone, with a good clinical response and initial regression of the lymphadenopathy and skin lesions. However, when the steroid dose was reduced, the patient's skin lesions and lymphadenopathy tended to recur, preventing complete withdrawal. Therefore, two cycles of Rituximab 1,000 mg were carried out with a 15-day interval between them, with the aim to avoid the side effects of prolonged corticosteroid use. The patient progressed with an excellent response to the immunobiologic. The corticosteroid was completely withdrawn. Rituximab was maintained every 6 months for control.

c) Discussion

The pathogenesis of IgG4-related disease is not yet fully understood, but it is presumed to be an autoimmune disease. Some autoantigens have already been proposed, such as galectin 3, laminin 111 and annexin A11, but further studies need to be carried out to better confirm this6-8. The CD4 + cytotoxic T

lymphocyte appears to be of fundamental importance in the pathogenesis, being found in large numbers scattered among the lesions of the affected organs9. Through the production of granzyme B, perforin, IL1, TGF beta and gamma interferon, CD4 + cytotoxic T cells appear to act on the fibrosis often present in this disease10. Another cell that has ained importance in the pathogenesis are T Helper follicular (Thf) cells, which help in the differentiation of B cells. Thf cells are increased in affected tissue and in peripheral blood, the concentration of which is related to disease activity[11].

Currently, it is postulated that the TH2 response, previously considered the main pathway in the etiology of IgG4 syndrome, plays a marginal role in the pathogenesis of the disease and is seen more frequently in atopic patients12. It should be noted that IgG4 syndrome has been better understood and studied recently, so it is believed that new discoveries regarding pathogenesis will occur over time.

It is described in the literature that IgG4 syndrome, in addition to organ involvement, can present non-specific subacute symptoms and influence the patient's general condition5. Furthermore, it usually involves two or more organs, which can be impacted synchronously or metachronously1. The skin is not a site commonly involved in IgG syndrome4. Skin lesions were found in 4.2% of patients in a study of 118 Chinese affected by the disease and in 6.3% in a study of 80 Japanese patients13,14 In the case described, the affected sites were the skin and lymph nodes, in addition to nonspecific symptoms such as malaise and loss of weight were present, characterizing involvement beyond the specific organ.

Lymphadenopathy is commonly present in IgG-related disease4 and can be generalized or localized. Generally, the lymph nodes do not grow more than 2 cm nd patients remain afebrile[15]. Lymph node involvement is typically observed together with other clinical findings of the syndrome but may be the initial or only manifestation of the syndrome[16]. The mediastinal, hilar, intra-abdominal and axillary chains are the main sites of lymph node involvement, and multiple lymph node chains are usually impacted[17].

The clinical picture of skin involvement is poorly described compared to that of other classically affected organs. However, when present, skin lesions present as nodules, papules or plaques which may be pruritic, preferentially affecting the head and neck and, less commonly, the trunk and extremities[15]. Skin involvement is strongly associated with lymph nodes -in 46% of cases-; lacrimal glands -in 33.3%-; orbit -in 30%-; and salivary glands -in 53%-. Autoimmune pancreatitis, on the other hand, is less common than is usually found in cases with cutaneous involvement[18].

Other differential diagnoses include skin lesions that can mimic nodular prurigo, rosacea, angiolymphoid hyperplasia with eosinophilia, xanthogranulomas and cutaneous lymphomas19 . Lymph node enlargement is often confused with lymphoma, sarcoidosis, multicentric Castleman's disease or other malignancies5. Therefore, a correct diagnosis is essential, excluding malignancies, so that the patient can have better clinical management and avoid unnecessary treatment.

In the case described, for both the cutaneous and lymph node involvement, different diagnostic hypotheses were previously proposed until the correct diagnosis was reached. The skin lesions had previously been diagnosed as nodular prurigo, polymorphous light eruption and rosacea, which is part of the differential diagnosis reported in the literature. On the other hand, in the differential diagnosis of lymph node involvement, the lymphoproliferative neoplasms have been suggested, as well as infectious diseases with lymph node involvement. Against this backdrop, it is important to know more about the syndrome IgG4 so that it can be better understood, enabling clinical suspicion and early diagnosis.

In 2019, the American College of Rheumatology submitted a classification and criteria for the diagnosis of IgG4-related disease. Until then, the proposed criteria were based on three pillars: 1) characteristic clinical criterion of swelling or mass with involvement of one or more organs; 2) hematological criterion with presence of serum IgG4 > 135 mg/dL; 3) histological criterion with presence of lymphoplasmocytic infiltrate and fibrosis added to a ratio of IgG4+/igG+ plasma cells greater than 40%, in addition to the visualization of more than 10 IgG4+ plasma cells per high magnification field18 . The presence of criteria 1, 2 and 3 confirms the diagnosis, the presence of criteria 1 and 3 makes the case probable and the presence of criteria 1 and 2 makes the case possible. Therefore, it should be emphasized that an increase in serum IgG4 levels is not necessary or specific for the diagnosis 20, 21. Although histo-pathology is considered by some authors to be the gold standard test, it should not be evaluated in isolation from the context of a patient with clinical signs suggestive of IgG4- associated disease.[21]

In skin or lymph node biopsies, you don't necessarily find all the classic histopathological findings. The expected findings described in the literature include a dense lymphoplasmocytic infiltrate rich in IgG4, obliterative phlebitis and storiform fibrosis. However, these findings can vary according to the organ affected and the patient. Histopathology of the skin usually shows a lymphoplasmacytic infiltrate in the dermis and/or subcutaneous tissue, with perivascular and perianexial involvement. Obliterative phlebitis and a storiform pattern of fibrosis are rarely present. The lymph nodes also often don't show the clinical signs described, such as storiform fibrosis 15,21.

In the case of the patient under study, the skin and lymph node biopsies did not show the 3 classic findings. The lymph node biopsy was able to rule out

evidence of malignancy and the infectious diseases considered. The histological criteria were better met with a skin biopsy of the right axillary region, which showed a significant lymphoplasmocytic infiltrate. Subsequently, this biopsy Immunohistochemistry was carried out on the skin, which revealed positivity for CD138 plasma cell antigen and more than 30 IgG4+ cells per high magnification field.

Imaging tests can help to corroborate clinical and histopathological suspicions, elucidate the involvement of the disease, and are useful for better choosing biopsy sites and helping with patient follow-up. These tests include ultrasound (USG), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET-CT)[5,22]. As it is a disease with the potential to affect several organs, the active search for other affected sites should be encouraged. In the case studied, the CT scan was of great importance as it revealed the involvement of numerous lymph node chains, although the presence of the disease in organs other than the skin and lymph nodes was not found.

In IgG4-associated disease, some complementary tests may be found to be positive more often than in the general population. These include those that are frequently positive — in more than 50% of cases — which can be increased IgG4, IgG or IgE; those that are commonly positive — found in 25 to 50% of cases — such as FAN, rheumatoid factor and complement drop; and those that are uncommon — in less than 25% of cases, such as increased CRP[1]. In the case under study, the patient had an increase i n serum IgG and IgG4, a FAN pattern of 1/640 (homogeneous) and a drop in C4, which is in line with what has been reported in the literature without this meaning another disease.

Other studies defend the importance of plasma blasts, which are an oligoclonal population of CD19+ CD20- CD27+ CD38+, precursors of tissue antibodies. Plasma cells are increased in active disease, which can be seen using flow cytometry. For some authors, the plasma blast count correlates with the activity of the disease and, with the When treatment is started, the value decreases and, in the presence of relapses, the value increases more reliably than IgG4 levels[4,5]. The plasma blast count, however, is not universally available in practice and, for the same reason, could not be carried out on the patient reported.

The criteria proposed by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) in 2019 establish the need for involvement of an organ typically affected in the syndrome, exclusion of other etiologies for the case and laboratory evidence of IgG4-RD (serological, histological, imaging)[27]. Our patient had lymph node and skin involvement. As already mentioned, the skin is not a frequently affected organ. On the other hand, lymph node involvement is frequent, as is skin involvement associated with lymph node involvement [18,28].

With regard to treatment, a consensus supports the idea that systemic corticosteroids, when indicated, are the first line of therapy for inducing remission. Generally, the equivalent prednisone dose of 0.6 mg/kg/day is given initially, and lower doses can be administered in maintenance therapy to prevent relapses when necessary. Azathioprine (2 mg/kg/day), Mycophenolate (up to 2.5g/day) and other immune-suppressants appear as second-line treatment with the aim of maintaining remission and avoiding the damage secondary to prolonged steroid use[5,15]. Although corticosteroid sparing agents are frequently used in cases of autoimmune pancreatitis and sclerosing cholangitis related to IgG4 syndrome, more studies need to be carried out to better evaluate the efficacy of these medications [23,24,25].

Rituximab (anti-CD20) has recently been reported as a promising treatment for IgG4-associated disease, probably acting on plasma blasts, reducing IgG4 production and disease activity [5,15]. An intravenous dose of 1 g every 15 days for a total of 2 doses is the dose initially suggested for Rituximab, which has been shown to be effective both in inducing remission and in maintenance [26].

II. Conclusion

Based on the theoretical arguments discussed, it can be concluded that this was a case of IgG4-related disease that manifested itself clinically with involvement skin and lymph nodes. The diagnosis was made by combining clinical, histopathology, immunohisto-chemistry and other findings in blood and imaging tests. As this entity has only recently been described in the literature, much remains to be discovered about the pathogenesis, management and long-term outcome of patients with this disease. Therefore, further studies are needed to gain a better understanding of igG4- related disease.

With this case, we emphasize that in the case of papulonodular lesions and large masses of adenomegaly, skin biopsy can be a valuable and easily accessible tool for diagnosing IgG4 syndrome, ruling out neoplasms, avoiding inappropriate management or a late diagnosis.

III. Attachments

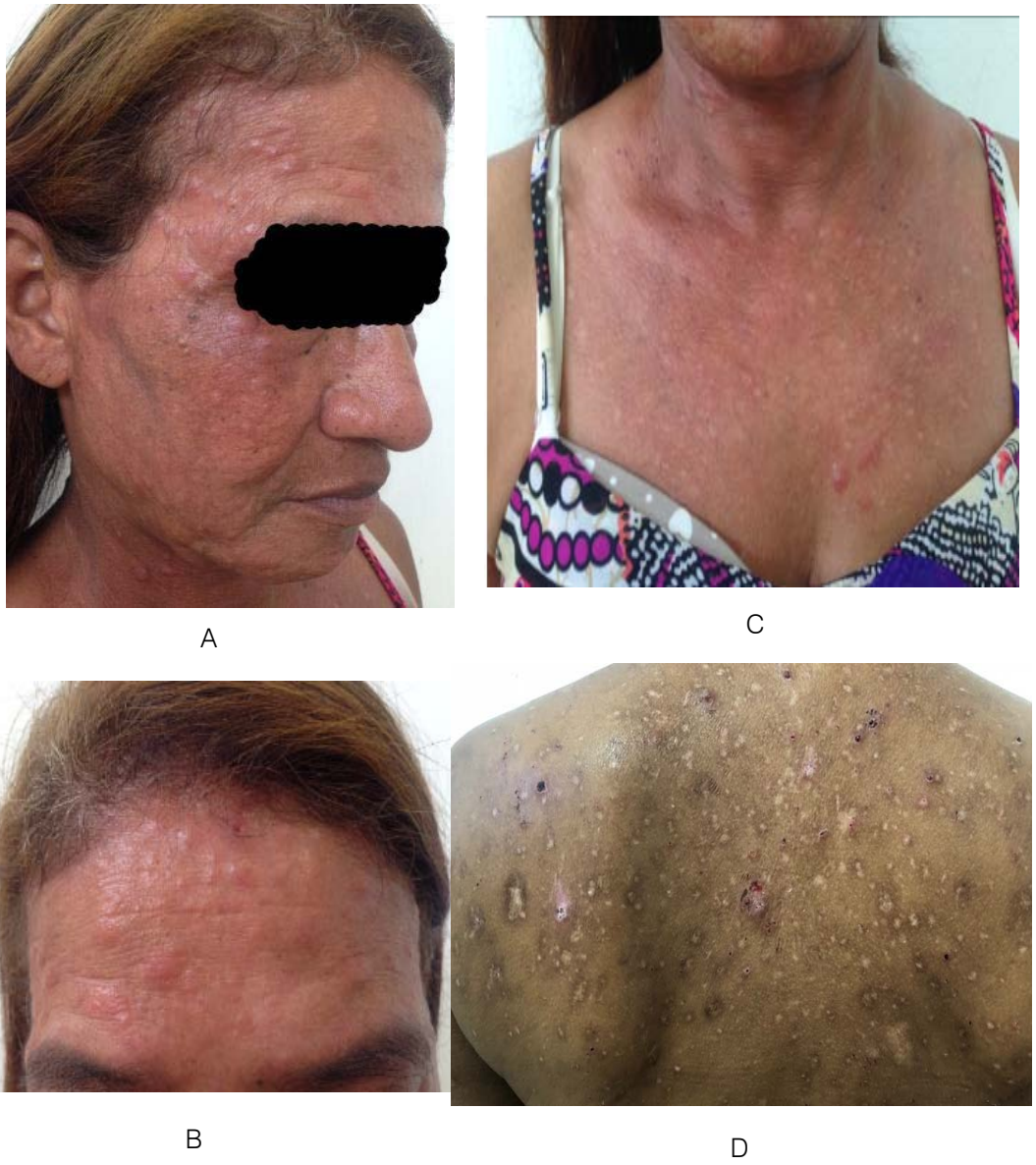
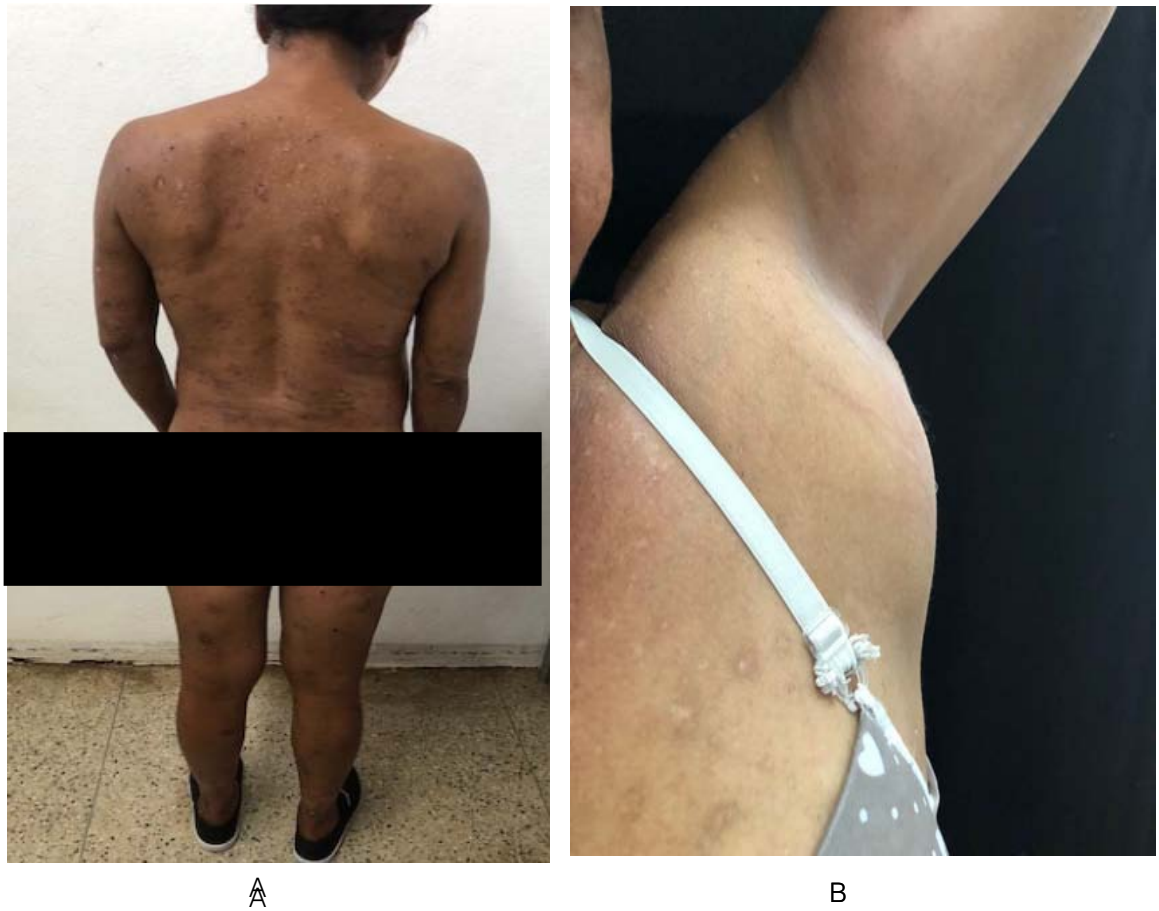
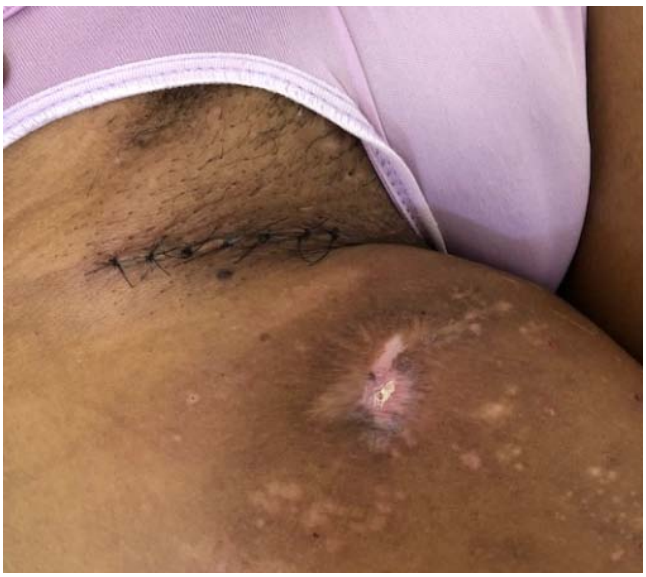


Fig. 1: (A and B) Presence of erythematous papulo-nodular lesions affecting the face and cervical region; (C) Presence of papulo-nodular lesions affecting the neck and evidence of post inflammatory hypochromia lesions in the same topography; (D) Predominance of residual dyschromia on the back.

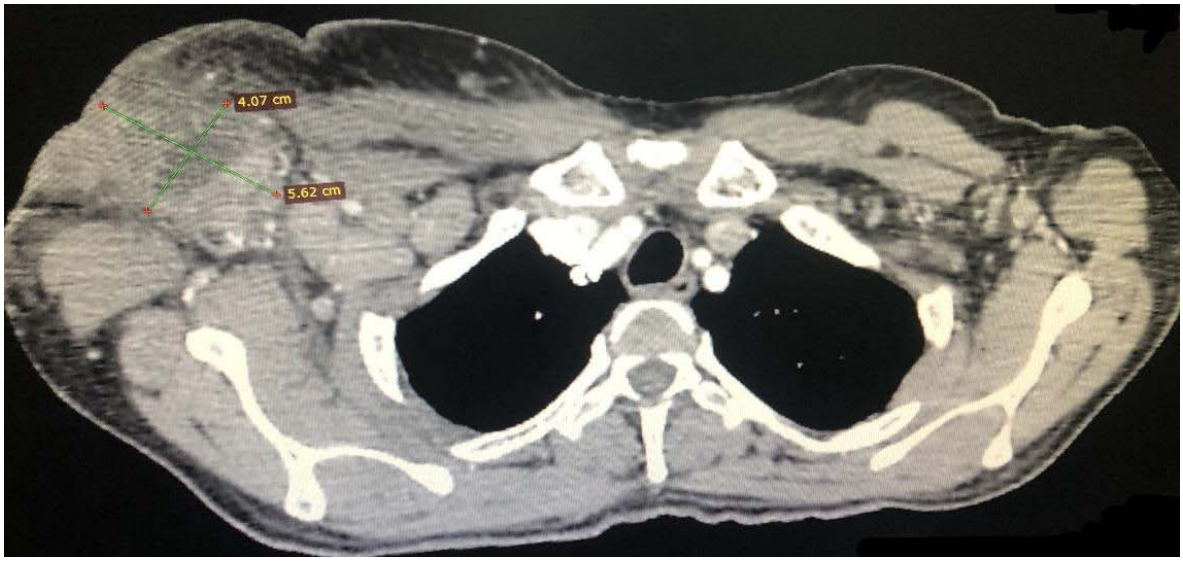


A B



C

Fig. 2: (A) Extent of skin involvement with a predominance of residual dyschromias; (B) Evidence of lymphadenomegaly with mass effect in the left axillary chain; (C) Lymph node biopsy site in the right inguinal chain.



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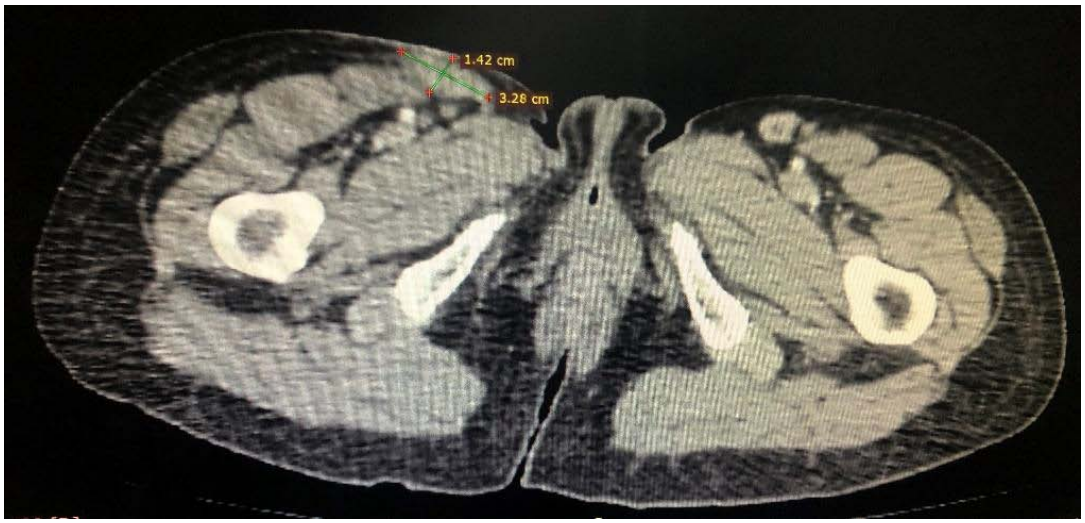

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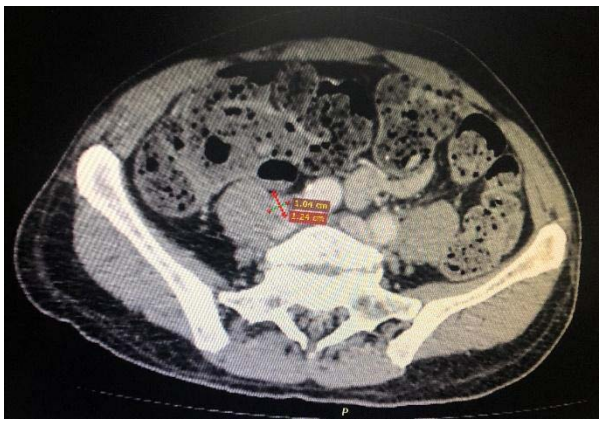
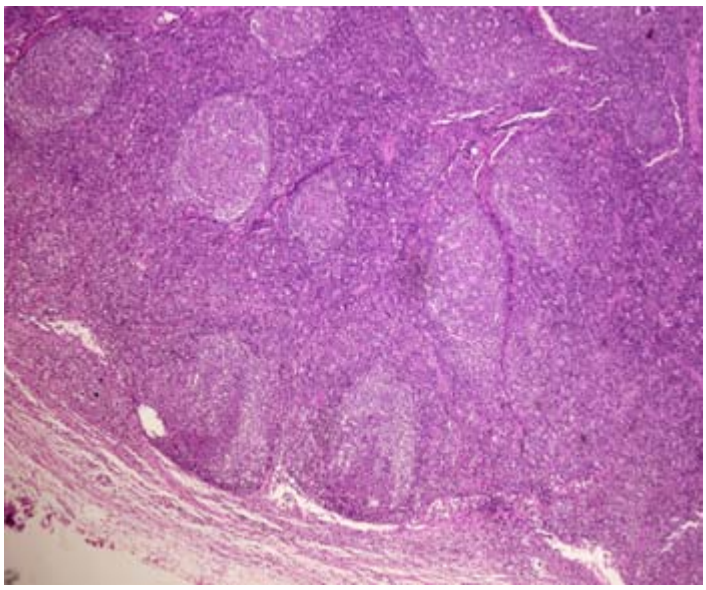


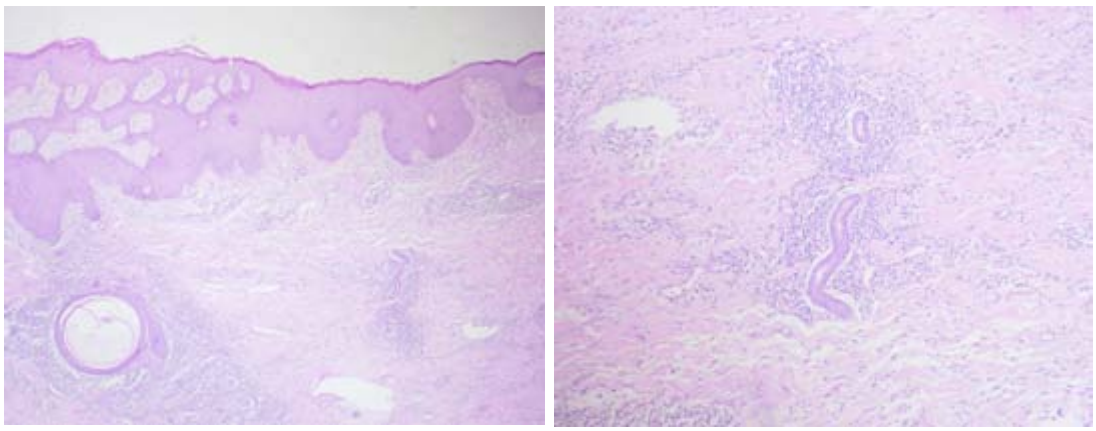
C

Fig. 3: (A) CT scan of the right axillary region showing confluent lymph nodes forming a mass with a necrotic center measuring approximately 56 x 40mm in its largest diameters; (B and C) CT scan showing lymphadenopathy in chains in the right inguinal region and the right common iliac region respectively.

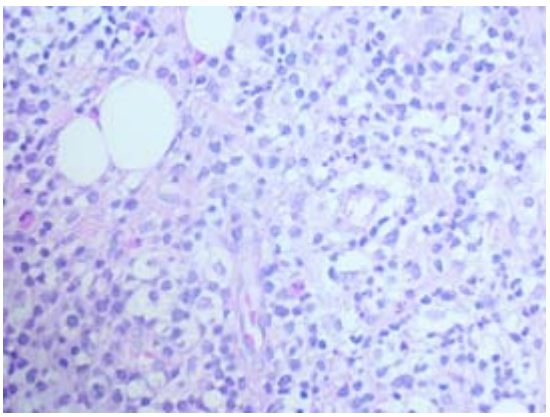


AB

Fig. 4: Reactive lymphadenopathy with a pattern of follicular and paracortical hyperplasia, with no evidence of neoplasia

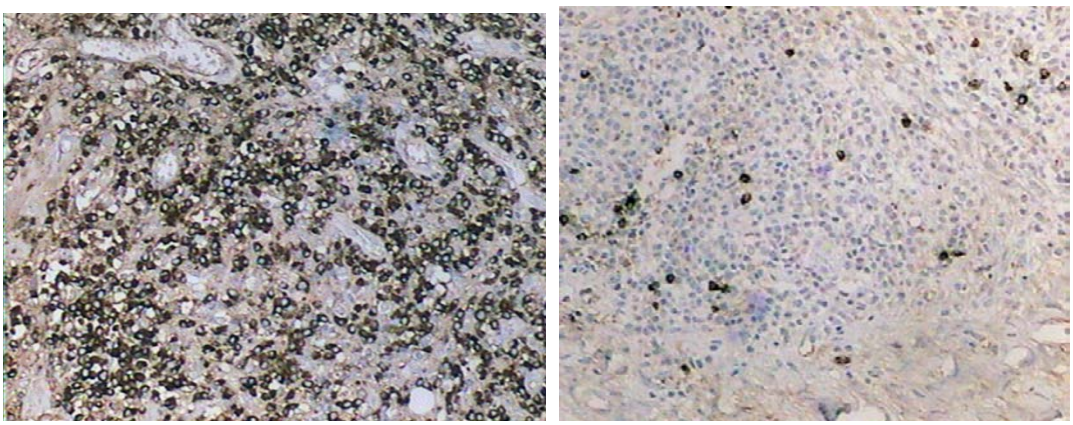


A B



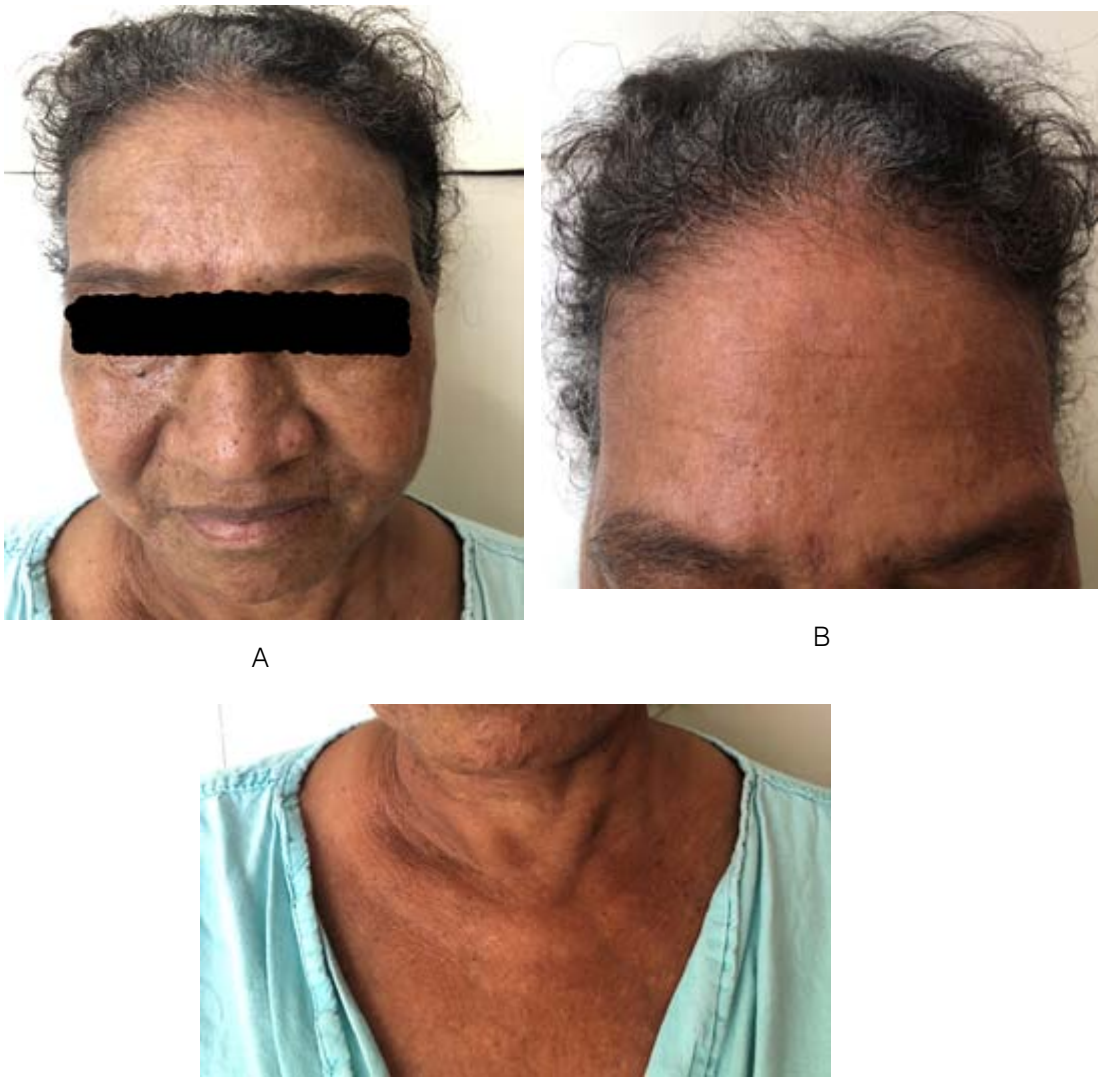
C

Fig. 5: (A) Lower magnification showing epidermis with irregular pseudoepitheliomatous acanthosis; (B and C) Dense inflammatory infiltrate made up predominantly of lymphocytes, plasma cells and histiocytes, permeated by some neutrophils and rare eosinophils, with no signs of parasites



A B

Fig. 6: (A) Immunohistochemistry positive for CD138 in plasma cells (Clone M115); (B) Immunohistochemistry focally positive for IgG4 immunoglobulin (Clone HP6025) - 30 IgG4+ cells per high magnification field



A B C

Fig. 7: (A, B and C) Remission of IgG4 syndrome-related skin lesions during prednisone maintenance at a dose of 40mg/day (0.6mg/kg/day)

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The Differences Males-Females all Doctors should Know About

By Maria Kuman, PhD

Editorial- In Eastern Asia, pulse diagnostics has been used before acupuncture treatments since time immemorial until today. All doctors practicing pulse diagnosis know that the pulse of males is stronger on the right hand and the pulse of females is stronger on the left hand, so they always check the pulse of males on the right hand and the pulse of females on the left hand [1]. Nobody ever explained why things are the way they were found to be, but I intend to explain this in this article. Also, all eye doctors should know that normally the right eye of males is stronger than the left eye and the difference is 0.25 diopter, while for females the left eye is stronger than the right eye and the difference is the same 0.25 diopter [2]. The eye doctors don't study this at the medical schools, and even after many years of practice, they usually don't have conscious awareness of this.

Why males' right side is stronger than the left and females' left side is stronger than the right? The Russian scientist Shkatov created and patented equipment that allows him to measure the spinning of the aura. He found that during the day: males' aura spins to the right (clockwise) and females' aura spins to the left (counterclockwise).

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Editorial

In Eastern Asia, pulse diagnostics has been used before acupuncture treatments since time immemorial until today. All doctors practicing pulse diagnosis know that the pulse of males is stronger on the right hand and the pulse of females is stronger on the left hand, so they always check the pulse of males on the right hand and the pulse of females on the left hand [1]. Nobody ever explained why things are the way they were found to be, but I intend to explain this in this article. Also, all eye doctors should know that normally the right eye of males is stronger than the left eye and the difference is 0.25 diopter, while for females the left eye is stronger than the right eye and the difference is the same 0.25 diopter [2]. The eye doctors don't study this at the medical schools, and even after many years of practice, they usually don't have conscious awareness of this.

Why males' right side is stronger than the left and females' left side is stronger than the right? The Russian scientist Shkatov created and patented equipment that allows him to measure the spinning of the aura. He found that during the day: males' aura spins to the right (clockwise) and females' aura spins to the left (counterclockwise). My lifelong studies of the aura found that the aura is nonlinear electromagnetic field (NEMF) [3]. Nonlinear physics teaches that vortices spin clockwise and suck energy and anti-vortices spin counterclockwise and emit energy. If so, during the day males' auras spin clockwise (to the right) like a vortex and suck energy through the top of their heads to get energized, which explains why males' right arm is stronger. During the day, females' auras spin counterclockwise (to the left) like an anti-vortex and sucks energy from the Earth to get energized, which explains why females' left side is stronger.

Why is the spinning of the aura so important? My lifelong studies of the aura found that the aura is emotionally sensitive - it shines brighter at positive emotions and it is dimmer at negative emotions. Since we say we are in high Spirit when we experience positive emotions and we say we are in low Spirit when we experience negative emotions, I concluded that the aura must be our Spirit. Then I found that the ancient Jewish Cabala was teaching to high priest that the aura is our Spirit. My lifelong studies of the aura found that the aura is weak NEMF, but it rules and regulates everything in the body, not with its strength, but with the information it carries, which means that the aura (Spirit) NEMF is weak informational field [4].

The fact that the aura (Spirit) rules and regulates everything in the body with the information it carries explains that: 1/ the clockwise (to the right) spinning of males' auras (Spirits) (during the day) make males' right hands more energized than their left hands, and 2/ the counterclockwise (to the left) spinning of females' auras (Spirits) (during the day) make females' left hands more energized than the right hands. The spinning of the aura (Spirit) also explains why the left hemisphere of the brain rules the right half of the body and why the right hemisphere of the brain rules the left half of the body.

I want to draw your attention to another interesting fact. The males button their cloths to the right, i.e. with the left side over the right, while female button their cloths to the left, i.e. with right side over the left. Nobody could explain why this is so. It has been this way since time immemorial. My explanation is:

1. Males button their cloths to the right because their aura (Spirit) NEMF during the day spins to the right like a vortex and sucks energy from Heaven through the top of their heads to energize them for the activities during the day. From here came the concept of Father God in Heaven. During the night, males' aura (Spirit) NEMF spins counter-clockwise and releases some of its NEMF energy to Heaven to prepare the males for the night-time rest and sleep [4].
2. Females button their cloths to the left because their aura (Spirit) during the day spins to the left like an anti-vortex and sucks energy from the Earth through their tail-bones like a vortex to energize them for the activities during the day. From here came the concept of Mother Goddess of Earth. During the night, females' aura (Spirit) NEMF spins clockwise and releases some of its NEMF energy to the Earth's NEMF to prepare the females for the night-time rest and sleep [4].

In conclusion, I must say that the auras (Spirits) of males and females spin in opposite directions in any time of the day or night, i.e. males and females have opposite magnetic polarities at any time of the day or

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require different medical treatments because not only their aura (Spirit) spins in opposite direction, their hormonal balance is different.

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Pulmonary Zygomycosis in a Patient with X-CGD

By Claudia Plech Garcia Barbosa, Matheus Cana Brasil Xavier da Silva, Rafael Burlacchini de Carvalho Magalhães, Victor Farias Coelho, Thainá Catão Lopes & João Carlos Coelho Filho

Abstract- *Objective:* To report a case of an X-CGD diagnosed patient presenting atypical zygomycosis. The X-CGD is a genetic disorder, autosomal recessive linked to the X, characterized by recurrent infections and granulomas formation.

Description: Male patient, five years, admitted at the hospital experiencing fever and shortness of breath for two months. The patient was hospitalized and given Ceftriaxone and discharged after improved clinical condition, butcontinued showing dyspnea and fever. The persistent clinical state demanded lung biopsy which revealed mucorales fungi.

Comment: This study has shown the importance of the correlation among infectious diseases from distinct pathogens in one individual.

Keywords: *chronic granulomatous disease; cgd; immunodeficiency; primary immunodeficiency; zygomycosis; fungal pneumonia.*

GJMR-F Classification: *LCC: RC280.S5, RC280.L8*

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Pulmonary Zygomycosis in a Patient with X-CGD

Claudia Plech Garcia Barbosa [α], Matheus Cana Brasil Xavier da Silva [σ], Rafael Burlacchini de Carvalho Magalhães [ρ], Victor Farias Coelho [ω], Thainá Catão Lopes[¥] & João Carlos Coelho Filho [§]

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I. Introduction

The pulmonary zygomycosis is an unusual fungi infection which occurs mostly in immunodepressive patients[11].In the CGD, the lung infection from fungi etiology is the one with higher prevalence, with the *Aspergillus* fungus as the more prominent reason[2].

Our report describes a patient with CGD plus pulmonary zygomycosis.

II. Case Report

Male patient, five years, coming from Alagoin has-BA, admitted at the hospital Martagão Gesteira (HMG) in Salvador-BA, diagnosed with pneumonia for five months and not responding to large spectrum antibiotic therapy. The patient developed fever and dyspnea five months back; he had received previous medical treatment in his hometown with the following antibiotics in sequence: Ceftriaxone and Oxacillin, Azithromycin, Tazocin, Sulfamethoxazole (plus Trimethoprim, Vancomycin, Meropenem and Fluconazole). The recurrent fever and tachypnea persisted, only the respiratory discomfort showed improvement.

The genitor denied knowledge on the disease although reported previous recurrent pneumonia since the patient was two-years old and abscesses episodes (1 scalp abscesses when newborn; 1 perianal and 1 cervical) that in turn led to many hospitalizations and previous use of antibiotics. Two maternal cousins were reported deceased in the family.

Regarding physical examination, low stature (Z-2 Height) and very thin (BMI Z-2), presenting tachypnea (40 BPM), SaO2 at 92% in room air, widely distributed murmur with crackles, mild intercostal retractions.

Examinations results held at reference hospital:

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Computerized tomography (CT) of the chest (FIGURE 1)

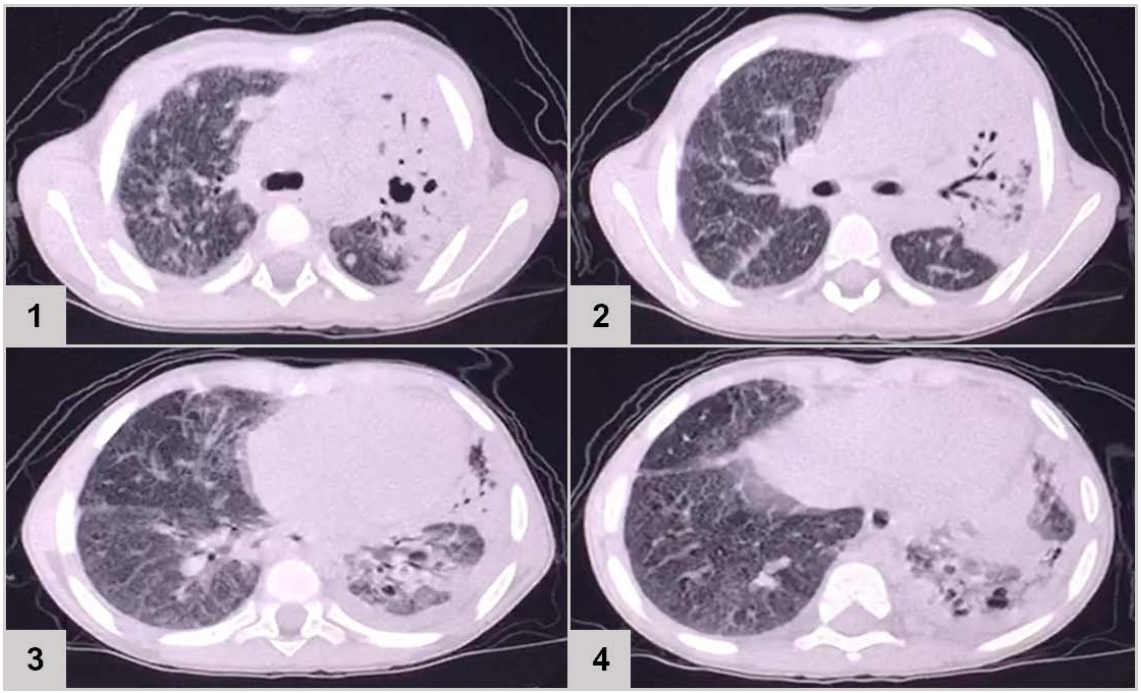

Figure 1: CT of the chest results: extensive consolidation, with air bronchograms and cystic images in between, in the left lung (3 and 4); ground-glass opacities, diffusion in the lower left lobe (1 and 2); nodular opacity, no sign of calcification in between, on both lungs (1, 2 and 3); reticular and linear opacity and parenchymal bands in the upper lobes (3 and 4); small pleural effusion on the left (1 and 2); adjacent subsegmental atelectasis (2 and 4)

Hemogram: hemoglobin: 10g/l; White blood cell count: 9400/mm^3; lymphocytes: 1692/mm^3; neutrophils: 7144/mm^3; eosinophil:188/mm^3; platelets: 425.000/mm^3. Negative blood culture. PPD no reaction. Normal range for Alpha-1 antitrypsin. Negative HIV. Normal sweat chloride values.

Primary immune evaluation (dose of complement, serum immunoglobulin and immune-phenotyping) all set in normal values for the patient's age.

Lungbiopsy (FIGURE 2)

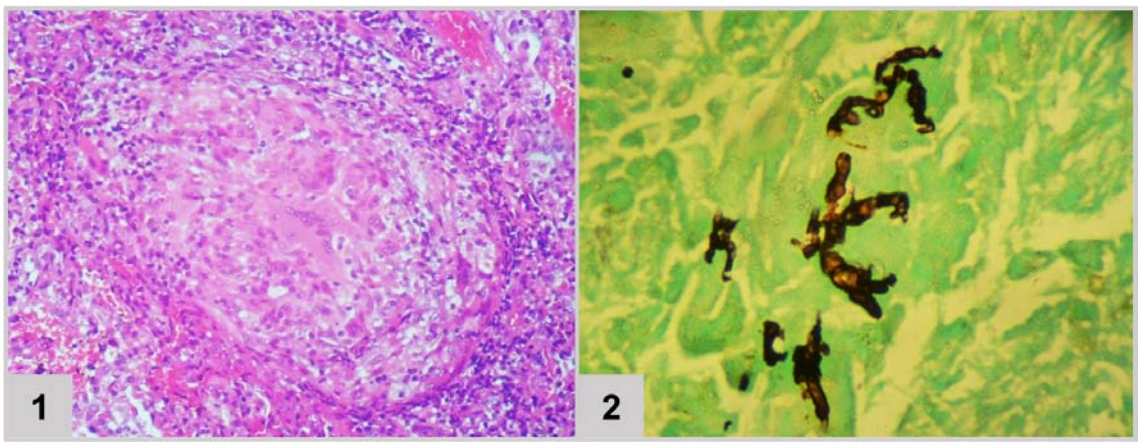

Figura 2: Lung biopsy (200x magnification). (1) Pulmonary tissue in hematoxylin and eosin showing granulomatous reaction with epithelioid histiocytes and multinucleated giant cells. (2) Pulmonary tissue in Grocott's stainrevealing fragments of broad, wavy and short hyphae, matching Zygomycosis by mucorales, longitudinal and cross-sectioned

With the fungal lung infection diagnosis (zygomycosis), without previously response to Fluconazole, Amphotericin B was administered. The fever disappeared and there was no need for supplemental oxygen, the patient was discharged from the hospital with mild tachypnea.

With the medical record of pneumonia and recurrent abscesses, as well as fungal pneumonia, Bactrim and Itraconazole were prescribed as a prophylactic measure anda dihydrorhodamine test (DHR) was ordered to evaluate the oxidase burst of phagocytes.

DHR test has revealed no sign of oxidation after stimulation with phorbol myristate acetate, PMA (from 59,2 to 48,1) has shown in comparison with the threshold an increase (from 34,7 to 91,6) which in turn confirmed the Chronic Granulomatous Disease (CGD) diagnosis. The antibiotic and antifungal prophylaxis has demonstrated good evolution and weight-stature gain (reverting FTT), the patient is listed for transplant.

III. Discussion

The CGD is an innate immunity disorder that is inherited, mostly characterized as an X-linked recessive mode, marked by the presence of two early childhood deaths of first-degree male cousins in the patient's family history (FIGURE 3).

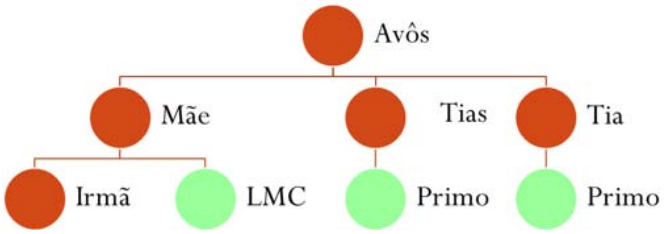

Figure 3: Patient Family history showing two childhood deaths of first-degree male cousins

This transmission pattern has been present in approximately 67%[1]of cases, more prominent and susceptible in male sex, linked to mutations in the CYBB gene, located on locus Xp21.1[1], which cause a functional deficit of gp91-phox, an enzyme complex component NADPH oxidase of phagocytes. This protein complex is responsible for producing oxygen metabolism intermediates in phagocytes, including oxidants with antifungal and antibacterial action.

Phagocytes, neutrophils, monocytes, macrophages and dendritic cells are cells capable of binding to pathogens and providing phagocytosis of these, through trapping within a phagosome. Several mechanisms, such as the release of lysozymes, acid hydrolases and toxic oxidants, are used by these cells of the immune system to destroy the pathogen. To carry out the production and release of oxidative compounds, phagocytic cells are able to assemble NAPH-oxidase complexes in the phagolysosome membrane, which are responsible for catalyzing the production of these compounds[13]. The protein complex provides the generation of O^{2-}, which is unstable and has a weak bactericidal action, through the transfer of electrons from intracellular NADPH molecules to molecular oxygen. The generated O^{2-} will later undergo dismutation reactions, catalyzed by the enzyme superoxide dismutase (SOD), which will convert it into hydrogen peroxide (H_2O_2). Finally, the enzyme myeloperoxidase (MPO) present in primary granules (mainly from neutrophils) is released into the phagosome and converts H_2O_2 into oxidants with great bactericidal power, reactive oxygen species (ROS), such as hypochlorous acid and radicals free (such as OH^- and O^-)[14]. After activation and assembly of the complex, the phagocytic cell enters a transient stage of oxidative explosion, where there is a significant increase in oxygen consumption[13].

Thus, CGD patients possess dysfunctional neutrophils and incapable oxidative burst, which in turn disable catalase-positive and intracellular micro-organisms' elimination[11]. There is also granuloma formation, mostly sterile, a characteristic that may be directly connected to the hyperinflammatory state common in CGD patients[10]. Granuloma is a means of containing the proliferation of the microorganism that is difficult to eliminate and isolating it from the rest of the organism[10].

Morphologically, granulomas in patients with CGD, in general, have the following histopathological organization:

- Neutrophils located predominantly in the central portion, with extremely reduced activity and some even in the apoptotic phase.
- Lymphocytes located both in the central and peripheral portions, being highly induced to apoptosis.
- Macrophages located essentially in the peripheral portion, usually with high expression of TNF-alpha cytokines, which recruit and induce the action of inflammatory cells, IL-10, which inhibits the function of neutrophils and induces cell healing and the IDO enzyme (Indoleamine 2, 3-dioxygenase), which converts L-tryptophan, an important bacterial substrate, into L-kynurenine, a protective inflammatory agent that induces apoptosis in lymphocytes.

- Epithelioid cells located in the central portion of the granuloma are modified, squamous and almost dysfunctional macrophages, due to their intense activity in the attempt to remove the infectious agent that is difficult to eliminate. Multinucleated giant cells, formed from the fusion of epithelioid cells, can also be observed.

Those are patients with a phenotype of life-threatening early life infections[1], where diagnosis usually occurs between 2 and 3 years, and more aggressive. Our patient had shown abscesses and pneumonia since his first months of life, weight-stature gain compromise.

As the individual with CGD has dysfunctional phagocytes, catalase-positive microorganisms become difficult to eliminate by the immune system, so that the patient diagnosed with CGD has a tendency of developing several infections through life; pneumonia is the most infectious and prominent, followed by lymphadenitis, suppuration, infectious dermatitis and abscesses formation in the skin, lungs, brain and liver, as well as osteomyelitis, meningitis and sepsis. There has also been manifestation related to the obstruction of gastrointestinal and urinary tract due to granuloma formation[2].

On the one hand, the most common gram-positive bacteria are Staphylococcus aureus and Nocardia spp. On the other hand, gram-negatives which stand out are Serratia marcescens, Burkhoderia cepacia e Klebsiela pneumoniae[1,2].

The most frequent fungus in CGD is the Aspergillus spp., constantly associated with pneumonias (generally the most prevalent agent), osteomyelitis, suppurative lymphadenitis, and also lung and brain abscesses[2].

Our patient had persistent pulmonary infection by fungi of the Mucorales order (Zygomycosis), a rare fungal type whose pathogenicity consists of the invasion of blood vessels of infected tissues, resulting in infarction and tissue necrosis[12].

The patient's chest CT scan for the evaluation of pulmonary zygomycosis showed suggestive findings of fungal balls in both lungs, visualized as non-calcified nodular opacities and pleural effusion on the left, which is an infrequent radiological sign[6], but of great importance for diagnosis, because the mutual presence of multiple fungal balls with pleural effusion are independent predictors of pulmonary zygomycosis[5].

The identification of the etiologic agent was possible through microscopy (FIGURE 2) that showed granulomatous tissue, and, through Grocott staining, fragments of hyphae compatible with Mucorales fungi. Histopathological examination represents the most reliable method for diagnosing pulmonary zygomycosis[6]. Direct histomorphological visualization allows differentiation between Zygomycetes (short, tortuous broad hyphae of variable caliber with random branching at right angles) and Aspergillus fungi, and is extremely important because, clinically, lung infections caused by these fungi are indistinguishable[7].

In this case report, the patient's clinical improvement was achieved after taking Amphotericin B, the drug of choice for zygomycosis therapy[4]. This drug is available from the Ministry of Health in two formulations: Amphotericin B deoxycholate (lower cost and higher toxicity) and Liposomal Amphotericin B (higher cost and lower toxicity), both with high efficacy. The starting dose tends to be 5 mg/Kg/day, usually increasing to 10 mg/Kg/day, much higher than the usual dose (1.5 mg/Kg/day), and therapy should be continued until there is complete resolution of clinical and radiological signs of infection[12].To avoid the toxic effects of Amphotericin B, especially on the kidneys, bone marrow, and cardiovascular system, the use of the later less toxic liposomal form is indicated[3].

Posaconazole is an important therapeutic alternative, since it also has activity against zygomycosis. Itraconazole has low effectiveness, while other azole antifungals, such as fluconazole and voriconazole, as well as flucitocin and echinocandin, are ineffective against mucorales fungi[4].

The diagnosis of CGD should be suspected in patients with a family history of first-degree relatives with early death, clinical history of severe infections (pneumonias, abscesses, osteomyelitis, lymphadenitis) and recurrent, early onset infections by catalase-positive germs, and it can be confirmed by biochemical tests which evaluate the oxidative function of phagocytes. In this report, measurement of superoxide anion production using the dihydrorhodamine (DHR) method demonstrated that after stimulation with PMA there was no oxidative burst (increased production of superoxide) in the phagocytes[8].

Prophylactic treatment is indicated for CGD patients to prevent fungal and Staphylococcus infections in addition to removing sources of pathogens. The recommended prophylaxis for these patients is a daily oral regimen of Sulfamethoxazole + Trimethoprim and Intraconazole, but since the latter drug has low activity against mucorales fungi, a substitution with Posaconazole may be considered. The patient should continue to receive routine vaccinations, except those containing live bacteria[1].

If a patient has pneumonia that is unresponsive to broad spectrum antibiotics, an investigation for fungal pneumonia should be extended to indicate specific treatment, and immunologic investigation in the care of a specialist for innate immune error should be initiated. Early diagnosis allows treatment of the infection as well as prophylactic management to decrease morbidity and mortality and discuss bone marrow transplantation, improving chances of survival and quality of life.

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Conflict of Interest

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Advancements in Morphological Verification: Evaluating a Novel Method for Pancreatic and Distal Bile Duct Tumour

By E. B. Revazov, Ts. S. Khutiev, M. R. Revazova, A. N. Chetiev, M. A. Kokoev, & G. S. Doev

Annotation- *The Aim of the Investigation*: Increasing the effectiveness of methods for morphological verification of tumours of the head of the pancreas (HP) and the distal common bile duct (DCBD) while reducing the risks of complications and reducing the time of diagnosis and treatment.

Materials and Methods: Retrospective analysis of treatment results of 441 patients with OJ of tumour origin. The results of endoscopic transpapillary and, or percutaneous transhepaticantegradeendobilliary minimally invasive surgical interventions in 439 (99.5%) patients were studied. An analysis of complications, causes and possible ways to eliminate them was carried out. The lack of technical capabilities, the complexity of implementation, the traumatic nature and risks of complications of using the existing arsenal of methods for obtaining histological materials from tumours of the HP and DCBD required the search for new solutions.

Keywords: *cancer, the head of the pancreas, distal common bile duct, obstructive jaundice, morphological verification, biopsy*

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E. B. Revazov [α], Ts. S. Khutiev [σ], M. R. Revazova [ρ], A. N. Chetiev [ω], M. A. Kokoev [¥] & G. S. Doev [§]

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Results: Primary transpapillary interventions for obstructive jaundice (OJ) were performed in 65 (14,8%), percutaneous puncture interventions – in 374 (85,2%) patients. The choice of method depended on the availability of technical capabilities. In incurable patients, we tried to solve the problem of OJ endoscopically. Antegrade decompression methods were more often used as a stage of treatment. Complications after endoscopic interventions on the Major Duodenal Papilla (MDP) developed in 20 (30,7%), after antegrade interventions – in 52 (14%). In both cases, the main problem was drainage dislocation, in 14 (21,5%) and 37 (9,9%), respectively. During antegrade interventions, the problem of drainage dislocation is solved by using drainages with a thread fixation of the inner ring. Minimally invasive decompression interventions at the first stage of treatment of patients with OJ tumour origin reduced the percentage of fatal postoperative complications to 2,0%. The first results of using the developed trephine biopsy method showed its high efficiency, reliability and safety.Morphological verification was obtained for all 8 patients. Cancer of the HP was confirmed in 6 cases, in 4 histologically and cytologically, in 2 – only cytologically. Chronic pancreatitis was detected in 2 patients. No complications were observed after using the trephine biopsy method we developed.

Conclusion: A differentiated approach to the biliary tract at the first stage is important for improving treatment results. For patients with the prospect of radical or palliative operations, percutaneous interventions are preferable. The use of the method of simultaneous puncture transhepatic bilioduodenal drainage with trephine biopsy of tumours of the HP and the DCBD is, in our opinion, a new promising direction in solving the problem of morphological verification of tumours of the hepatopancreatoduodenal zone and reducing the time for diagnosis and treatment of patients with OJ of tumour origin up to 7-8 bed-days. Preoperative knowledge of the anatomy of the tumour, its relationship to HC, duodenum according to MRI or CT is necessary for effective and safe trephine biopsy.

Keywords: cancer, the head of the pancreas, distal common bile duct, obstructive jaundice, morphological verification, biopsy.

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I. Epidemiology

Malignant tumours of the hepatopancreatoduodenal zone (HPDZ) account for 15% of tumours of the digestive tract. The pancreas accounts for up to 86% of neoplasms, and more than 60% are localized in the head of the pancreas [1]. Pancreatic cancer causes more than 331000 deaths in the world annually and

accounts for 40% of the total cancer mortality, ranking 7th in the world, 5th in Europe, 4th in USA [2]. According to preliminary expert estimates, by 2030 pancreatic cancer will become the second most common cause of death from malignant neoplasms [3]. This determines the relevance of the problem of early diagnosis and treatment of this pathology at the present time. Ductal adenocarcinoma accounts for 95% of HP malignancies and is the most common cause of OJ of tumour origin [4,5]. In second place is cholangiocarcinoma (CC), with an incidence ranging from 1 to 113 per 100000 population. The increase in the incidence of CC in Russia over the past ten years has increased and amounted to 26,64% [6,7].

OJ in malignant lesions of the HPDZ organs occurs in 36,6 - 47,0% of patients, in HP and DCBD cancer it reaches 95% [8,9,10]. A blurred clinical picture and lack of clinical follow-up lead to the neglect of the pathology. Accordingly, resectability for pancreatic head cancer is no more than 15-20%. [11].

Purulent cholangitis (PH) is one of the most common and severe complications of benign and malignant diseases of the biliary tract caused by a violation of their patency. The main etiological factor of cholangitis are cholestasis, infection and the phenomenon of damage to the common bile duct mucosa [12]. It is believed, that without surgical resolution, acute purulent cholangitis leads to death in 100% cases. Postoperative mortality, according to various authors, varies widely and ranges from 13 to 60% [13].

A wide range of studies are used in the diagnosis of tumour diseases of the HPDZ organs. Ultrasound examination is routine and quite informative [14]. However, a more detailed examination of the biliary tract allows contrast-enhanced MRI of the abdominal cavity with MRCP, including in the version of the hydropressive MRSP [15]. Another highly informative research method is contrast-enhanced multislice computer tomography (MSCT). It was found that an average in 70-85% of patients, the resectability of the tumourdetected using CT imaging was confirmed intraoperatively and is considered the gold standard for diagnosing cancer of the HP [16].

Endoscopic methods for examining the upper gastrointestinal tract are mandatory for diseases of the HPDZ organs [17]. The role of endoscopic retrograde cholangiopancreatography (ERCPG) is mainly therapeutic and is used to resolve jaundice [18]. ERCPG with transpapillary excisional biopsy showed a low detection rate of pancreatic head cancer (33-71%). According to some reports, the use of a method with accelerated cytological examination made (ROSE) it possible to increase sensitivity to 76-97% [19].

Confocal laser endomicroscopy (CLEM) is characterized by its effectiveness in treating tumour strictures at the initial stage of the process. But with its high efficiency (93,3%), high sensitivity – 91,7%, specificity – 93,8% and overall accuracy – 92,8%, when combined with choledochoscopy and biopsy, demonstrated labour intensity and high operator-dependence method [20]. Puncture fine-needle CLEM has shown high diagnostic value in the diagnosis of cystic diseases of the pancreas [21].

The use of SpyGlass increased sensitivity and specificity to 71 and 100%, respectively. However, the technique is very expensive, which makes it impossible to use in most public sector medical institutions [22].

The probability of developing pancreatitis and peritoneal dissemination of tumour cells limits the use of percutaneous pancreatic biopsy. Fine-needle aspiration biopsy (FNAB) under EndoUS control has the lowest complication rate of 1-2%. The method is especially valuable for tumours less than 2 sm. Moreover, the sensitivity and specificity of the method, according to the meta-analysis, are 85 and 98%, respectively. When atypical or suspicious cancer cytology was included, sensitivity increased to 91%, but specificity decreased to 94% [23]. However, this method also has high operator dependence, complex and lengthy specialist training, and high cost of equipment.

Despite the possibilities of modern high-tech diagnostic and treatment methods, postoperative mortality after one-stage operations against the background of OJ remains relatively high and it amounts to 15-40% for tumour jaundice [17]. Complications after percutaneous endobiliary drainage for OJ in 2,4-32,7% of patients, mortality – from 0,4 to 13,8% [24].

Endoscopic transpapillary interventions can resolve OJ in cancer of organs of HPDZ in more than 80% of cases. They make it possible to prepare patients with OJ for surgical interventions, including radical ones, or become the final methods of palliative treatment of HPDZ tumours complicated by OJ in inoperable patients [25]. In young patients with unresectable HPDZ tumours and OJ syndrome, with a life expectancy of more than six months, the choice of palliative internal bile diversion for distal biliary block is hepaticoenterostomy. In other clinical situations, using one of the methods of stenting the bile ducts is justified [26].

A combination of antegrade and transpapillary methods of decompression of the biliary tract, objective phasing of surgical treatment while observing the principle of an individual approach increases the effectiveness of treatment and reduces the percentage of complications and unfavorable outcomes.

The unsatisfactory results of chemotherapy for pancreatic cancer are due to the chemoresistance of this type of tumor for two reasons: the presence of very dense, poorly vascularized, fibrous tumor envelope and high expression of R-glycoprotein. This first makes it difficult to deliver the chemotherapy to the tumour, and then accelerates its elimination [3].

Regional methods of chemotherapy have shown their effectiveness. A combination of cycles of chemoembolization (CE) and chemoinfusion (CI) was the most effective method of intra-arterial therapy in patients with unresectable pancreatic cancer: the median was 15, 6 months compared with 11,7 and 10,8 months for CE and CI [27].

The probability of using targeted therapy in patients with pancreatic cancer based on molecular testing was 26%. Using it in this group of patients increased the median survival from the moment of disease progression to 31 months, compared to 18 months with standard chemotherapy [28].

Therefore, the current state of the problem of early diagnosis of pancreatic cancer, the lack of a simple method of histological verification with a low cost, dictates the search for new organizational solutions and scientific developments in this direction. Progress in drug therapy for pancreatic cancer makes the problem even more urgent.

II. Materials and Methods

An analysis of the treatment results of 441 patients with obstructive jaundice of tumour origin over 19 years was carried out.

Study Periods:

- 2000 - 2007the X-ray surgery department of the Republican Clinical Hospital, Vladikavkaz;
- 2014 - 2021 based on the surgical department of the Clinical Hospital of the NorthOssetian State Medical Academy;
- 2022-2024 surgical department of the State Budgetary Healthcare Institution "Republican Clinical Hospital of Emergency Medical Care" Vladikavkaz;
- 2023-2024 surgical department of the Suburban Central District Hospital in the v. Oktyabrskoye.

Innovative methods are approved for use in clinical practice after approval by the Ethical Committee at the North Ossetian State Medical Academy in 2018. All patients signed informed consent for the proposed therapeutic and diagnostic measures.

Of the treated patients, 223 (50,6%) were men, 218 (49,4%) were women.The age of patients was from 20 to 91 years. Average age – 69,5±0,97years, men – 69,4±1,3, women – 69,5±1,4 years (Fig. 1)

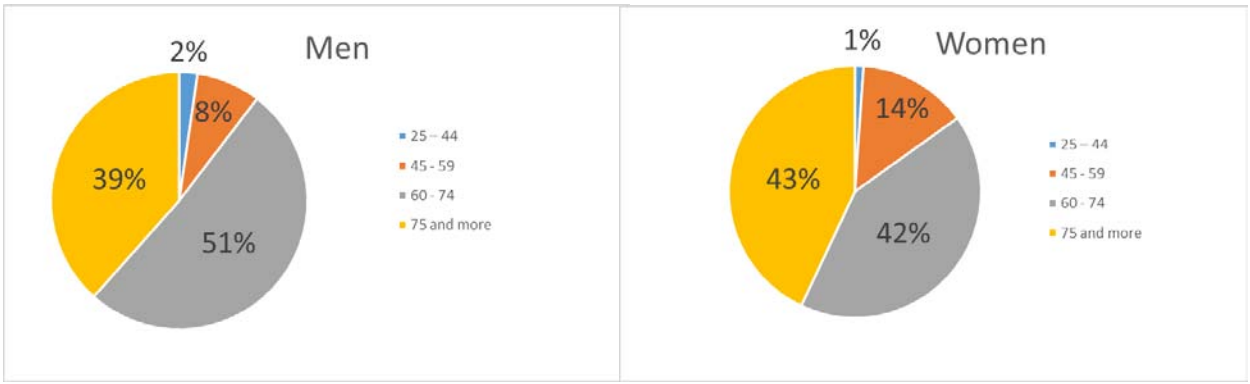


Fig. 1: The analysis of the treatment results of 441 patients with tumour genesis for 19 years

In the morbidity structure, the most common types were cancer of the head of the pancreas and Klatskintumour (Fig.2).

Localization	Number of patients (%)
The Head of the Pancreas	236 (53,3%)
Cancer of the GDP (great duodenal papilla) and DCBD (distal common bile duct)	58 (13,1%)
Klatskintumour	86 (19,5%)
Liver cancer	8 (1,9%)
Gallbladder	29 (6,6%)
Metastases at the gates of the liver	24 (5,6%)

Fig. 2: The structure of biliopancreatoduodenal cancer

The duration of the pre-hospital period from the moment the complaints appeared was on average 24,3±4,7 days.

The patients underwent clinical, labouratory and instrumental research methods: electrocardiogram, chest radiography, ultrasound of the abdominal organs, esophagogastroduodenoscopy, MRI of the abdominal

cavity with MR cholangiography, MSCT of the abdominal cavity with/without contrast enhancement, ERCP, percutaneous transhepatic cholangiography, fistulocholangiography.

Distribution of patients according to the level of bilirubinemia: mild (22 – 100 μmol/l) – 48 (10,9%), moderate (100 – 200 μmol/l) – 114 (25,8%), severe (200 or more μmol/l) – 279 (63,3%) patients.

Severe forms of acute cholangitis according to TG18 were detected in 169 (38,3%) patients: Grade II – 138 (32,4%), Grade III – 31 (7,3%).

Concomitant pathology was detected in 339 (76,9%) patients. The main share was made up of patients with cardiovascular diseases. Cardiac ischemia was diagnosed in 274 (62,1%) patients, and 93 (21,1%) patients suffered from type 2 diabetes mellitus.

We conditionally divided the patient into two groups: primary endoscopic (group I) and primary percutaneous (group II) interventions (Fig. 2).

The comparison of the groups was carried out for the period 2014-2019 when the possibility of both types of interventions became available. During the analysis, the average values M+mwere determined, where M – is the average value and m – is the standard error of the mean. The groups were representative according to Student's t-test ($p>0.05$) in terms of hepatorenal, hematosis function and the degree of cholangiectasia according to radiological research methods. Moreover, in the group with primary endoscopic interventions, patients with severe cardiovascular pathology prevailed. (Fig.3)

NN	Criterion	Group I (primary endoscopic interventions)	Group II (primary percutaneous interventions)
1	Total bilirubin	304,3 ± 39,1	264,8 ± 21,4
2	Aspartate aminotransferase	145,1 ± 15,6	135,7 ± 15,3
3	Alanine aminotransferase	212,0 ± 25,7	154,2 ± 19,8
4	Alkaline phosphatase	1103,4 ± 278,1	1563,9 ± 395,2
5	Prothrombin index (%)	84,5 ± 2,3	82,8 ± 1,8
6	Blood urea (mmol/l)	5,7 ± 0,4	6,45 ± 0,6
7	Creatinine (μmol/l)	90,6 ± 6,5	89,0 ± 4,6
8	Leukocyte ($x10^9$)	8,0 ± 0.5	9,0 ± 0.5
9	Thrombocyte (x1000)	288,2 ± 15,8	253,7 ± 14,5
10	Hemoglobin ($x10^{12}$)	124,1 ± 2,7	118,5 ± 2,9
11	Hepaticocholedochus diameter (mm)	12,8 ± 0,7	14,0 ± 0,6
12	Block level High Average Short Double	 9 (21,4%) 0 32 (76,2%) 1 (2,4%)	 19 (36,5%) 7 (13,5%) 25 (48,1%) 1 (1,9%)
13	Erosive and ulcerative lesions of the stomach and duodenum	6 (14,3%)	5 (9,6%)
14	Essential hypertension 2-3 stages	31 (73,8%)	33 (63,5%)
15	2A-B degree circulatory failure	18 (42,9%)	15 (28,8%)
16	Diabetes mellitus 2 type	6 (14,3%)	15 (28,8%)

Fig.3: Comparative characteristics of patients with primary endoscopic and percutaneous interventions [29]

During surgical treatment, preference was given to low-traumatic decompression surgical interventions. At a low and moderate level of block of extrahepatic bile ducts of tumour origin, in technically possible, we began with transpapillary interventions. When using antegrade decompression methods in isolation from 2000 to 2007, we adhered to the tactics of staged interventions (external, then external-internal drainage with an interval of 7-8 days). Subsequently, we tried to perform one-stage external-internal drainage with endoscopic papillosphincterotomy (EPST). The tactic of phasing is preserved only in patients with purulent cholangitis.Symptomatic therapy was prescribed to patients with Klatskintumour, Bismuth 4. Conservative treatment included detoxication, hepatoprotective therapy, correction of water and electrolyte disorders, and treatment of concomitant diseases.

For the purpose of cytological verification, antegrade and retrograde methods of brush-biopsy of the area of tumor strictures of the bile ducts and fine-needle aspiration-cutting biopsy of tumor formations were used. To obtain histological material, endoscopic excisional biopsy, percutaneous biopsy using semi-

automatic needles or an automatic biopsy system were used.

III. The Results

439 (99,5%) patients received surgical treatment and 2 (0,5%) patients could not be prepared for surgery due to the severity of the condition. In total, 719 operations were performed, which amount to1,64 operations per patient (Fig. 4). The choice of method depended on the availability of technical capabilities at the current time. In incurable patients, we tried to solve the OJ problem endoscopically.

Type of operation	Quantity
Endoscopic	
Atypical (incisional) papillotomy	5 (7,7%)
EPST	9 (13,8%)
Bilioduodenal stenting	43 (66,1%)
Nasobiliary drainage	1 (1,5%)
"Rendezvous" technique	12 (18,5%)
Percutaneous	
Primary percutaneous transhepatic external drainage of the bile ducts (PPTEBD)	303 (83,6%)
Separate external drainage	39 (12,9%)
Of which: Drainage of one lobe of the liver Separate sub-sectional drainage Separate segmental drainage	15 (38,5%) 21 (53,8%) 3 (7,7%)
Percutaneous transhepatic external-internal drainage of the bile ducts (PTEIDBD) Of them: Primary PTEIDBD The second stage after PPTEBD Failed PTEIDBD	266 (70,0%) 57 (21,4%) 205 (77,1%) 4 (1,5%)
PTEIDBD was simultaneously supplemented with EPST	14 (5,3%)

Fig. 4: Decompressive surgical interventions for OJ of tumour genesis

Primary interventions on the Major Duodenal Papilla (MDP) were performed in 65 (14,8%) patients. In 2 (3,1%) of them it was unsuccessful, in one due to a previous gastric resection for Billroth – 2 peptic ulcer, in the other due to tumour deformation of the duodenum due to a tumour of the head of the pancreas. In 5 (7,7%) patients an atypical (incisional) papillotomy was performed, in 9 (13,8%) they were limited to endoscopic papillosphincterotomy (EPST). Both types of operations were used for cancer of the MDP (which was diagnosed as a result of histological examination). This turned out to be enough to relieve OJ and prepare patients for the second stage of the operation. In 43 (66,1%) patients,bilioduodenal stenting was required for adequate decompression of the bile ducts. In all cases, a plastic stent with a diameter of 8 to 12 Fr, more often 10 Fr, was used. In 1 (1,5%) patient, EPST was supplemented with nasobiliary drainage. The "Rendezvous" technique was used in 12 (18,5%) patients. The need arose due to the impossibility of cannulation of the MDP in patients with the presence of transhepatic drainage.

With a high block of the bile ducts, the presence of cholangitis, as well as with a medium and low block in the case of impossibility of endoscopic access or if there were indications for radical surgical interventions at the second stage, percutaneous decompression interventions were used. The presence of transhepatic drainage facilitated the formation and ensured decompression of biliodigestive anastomoses.

In total, 374 (85,2%) patients underwent percutaneous puncture interventions. It was unsuccessful in 4 (0,9%) cases in patients with Klatskintumour, Bismuth IV.

Primary percutaneous transhepatic external drainage of the bile ducts (PTEDBD) was performed in 303 (83,6%) patients. Of these, 264 (87,1%) with medium and low blocks achieved immediate complete decompression of the biliary tract. In 39 (12,9%) – with a high block involving the lobar bile ducts in the process of confluence, separate external drainage was used. Of these, 15 (38,5%) patients underwent drainage of one of the liver lobes. This was considered sufficient to reduce total blood bilirubin below 50μmol/l. If higher levels of bilirubinemia persisted, the second lobe of theliver was drainage. Separate sublobar drainage was performed in 21 (53,8%) patients, separate segmental drainage was performed in 3 (7,7%) patients.

Percutaneous transhepatic external-internal drainage of the bile ducts was performed in 266 (70,0%) patients, of which primary PTEIDBD in 57 (21,4%), the second stage after PTEDBD – in 205 (77,1%). In 4 (1,5%), it was impossible to pass the stricture area. In 14 (5,3%) PTEIDBD added with EPST. Analysis of literature data and experience in treating patients after transpapillary methods of bilioduodenal drainage allowed us to switch to primary PTEIDBD. In order to

prevent postoperative pancreatitis, especially in patients with absent or mild pancreatic hypertension, external-internal drainage was supplemented with EPST. This tactic made it possible to reduce water and electrolyte losses and shorten the length of hospital treatment.

Complication	Treatment
Endoscopic	
Dislocation of a plastic stent – 14 (21,5%)	Stent replacement – 12. Removal of the stent (cancer of the MDP) – 1. Conservative – 1.
Bleeding from a papillotomy wound – 6 (9,2%)	Electrocoagulation – 1. Conservative – 5.
Percutaneous	
Migration of bile drainage – 37 (9,9%)	Repeated drainage – 36. Laparoscopic drainage of the abdominal cavity with repeated PTEBD – 1.
Hemobilia – 5 (1,3%)	Correction of the position of bile drainage – 5.
Bile leakage into abdominal cavity – 6 (1,6%)	Puncture drainage of the abdominal cavity with correction of the position of bile drainage – 2. Translation PTEIDBD to external – 1. Laparotomy, sanitation and drainage of the abdominal cavity – 3.
Liver biloma – 1 (0,3%)	Puncture drainage – 1.
Compression of the left lobar duct by self-expanding stents – 1 (0,3%)	Puncture drainage of the left lobar duct – 1.
Pancreatitis – 2 (0,6%)	Conservative – 1.

Fig. 5: Complications afterdecompressive surgical interventions for bile ducts

Complications after endoscopic interventions (Fig.5) on MDP developed in 20 (30,7%) of 65 patients, in 3 (4,6%) two complications were noted. In 14 (21,5%) cases, there was stent dislocation due to an anatomical feature (angulation of the common bile duct) and incorrect choice of stent light. In 12 (18,5%) cases repeated stenting was required; in 1 (1,5%), the stent had to be removed due to the unstable position of the stent (angulation of the hepaticocholedochus, short distal stenosis);in 1 (1,5%) patient with an MDP tumour, at the time of complete dislocation into the intestine, the clinical manifestations of cholangitis were relieved and did not require additional interventions. Bleeding from the papillotomy site was observed in 6 (9,2%) patients;in 4 (6,1%), it was of moderate severity and was stopped conservatively; in 2 (3,1%) – severe bleeding was stopped by electrocoagulation of the bleeding vessel in 1 (1,5%) patient and conservatively – in 1 (1,5%). In 10 of 43 patients with bilioduodenal stenting, it was necessary to change the plastic stent due to its obstruction.The cause of obstruction was increased lithogenicity of bile and chronic cholangitis. The stent replacement period was varied from 5 to 90 days, averaging of 52,7$\pm$9,63 in two patients, two stents were installed during replacement.

The most common complication of percutaneous interventions was drainage dislocation in 37 (9,9%) patients, it was observed before the use of “Pigtail” drains with a thread fixation of the internal ring and in case of Klatskintumour, Bismuth 4. In all cases, repeated drainage was required, in 1 (0,3%) case, which was laparoscopic drainage of the abdominal cavity. Hemobilia developed in 5 (1,3%) cases, which was relieved by correcting the position of the bile drainage. All cases were at the stage of gaining experience in X-ray surgical interventions and were associated with an intrahepatic vessel falling into the trajectory of the bile duct puncture. In the future we tried to avoid such moments. Bile leakage into the abdominal cavity was observed in 6 (1,6%) patients, which required drainage of the abdominal cavity with correction of the drainage position in 2 cases, replacement of external-internal drainage with an external one in 1 patient, and laparotomy with sanitation and drainage of the abdominal cavity in 3 patients. In all cases, the cause was loss of adequate drainage due to drainage dislocation or obstruction. A liver biloma formed in 1 (0,3%) patient, which was drainage by puncture. In 1 (0,3%) case of a Klatskintumour after antegrade stenting of the bile ducts with self-expanding stent, compression of the left lobar duct occurred, which require additional its drainage. 2 (0,6%) patients developed mild pancreatitis, which was treated conservatively.

Out of 439 operated patients, 33 (7,5%) died, of which 23 (5,7%) died during the formation of X-ray surgical service. In 4 (0,9%) cases the cause of death was biliary peritonitis, all of them with a Klatskintumour, Bismuth IV. Progression of hepatocellular failure against the background of adequate decompression of the bile ducts was in 20 (4,5%) cases, acute cerebrovascular accident in 1 (0,2%) patient, progression of the underlying disease in 4 (0,9%) patients, pulmonary

embolism (PE) in 2 (0,4%) patients, bleeding from a growing tumour of the head of the pancreas in the duodenum – in 2 (0,4%) cases.

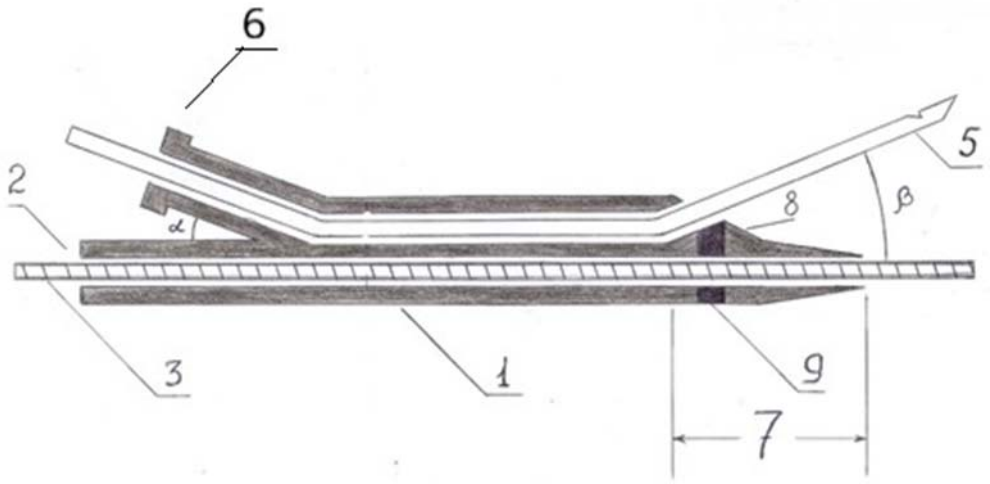
For the purpose of morphological verification oftumours of the head of the pancreas, the following were used: puncture trephine biopsy of a liver tumour – 6, transgastric trephine biopsy of a tumour of the head of the pancreas – 3, brush biopsy of the distal common bile duct for cancer of the distal common bile duct and head of the pancreas – 7 (3 – antegrade, 4 - retrograde), antegrade brush biopsy for Klatskintumour – 2, pinch biopsy for locally advanced cancer of the head of the pancreas and distal common bile duct and for cancer of the MDP in 19 patients. A brush biopsy of the distal common bile duct for cancer of the head of the pancreas and the DCBD gave three cheerful, two doubtful and two false-negative cytological conclusions. Transgastric trephine biopsy of a tumour of the head of the pancreas gave one false-negative result, in 1 case it was complicated by pancreatorhea.

IV. The Discussion

The lack of technical ability to biopsy tumours of the head of the pancreas and the distal common bile duct under EndoUS, performing CLEM and other expensive methods, the complexity and negative results of using transgastric trephine biopsy, the impossibility of obtaining histological material from brush biopsy led us to search for a safer, more effective and cost-effective an advantageous method for obtaining histological material from tumors of the HP and the DCBD.

We have developed and introduced into practical medicine method for trepan biopsy of tumoursof the head of the pancreas and the distal common bile duct and device (Fig. 6)for their implementation by E.B.Revazov–Ts.S.Khutiev(patent №№ 2722655, 2747591, 203409, 2768480). The essence of the invention is simultaneous percutaneous transhepatic external-internal drainage of the bile ducts with transcholangiostomy trephine biopsy of tumours of the head of the pancreas and the distal common bile duct and EPST (endoscopic papilla sphincterotomy) in patients with obstructive jaundice. We modified the antegrade method of core biopsy method[30] and used the principle of transjugular liver biopsy (percutaneous remote puncture biopsy with a flexible needle along a non-rectilinear trajectory with access through a tubular structure). The original deviceand method made it possible to provide trephine biopsy only under X-ray control. X-ray landmarks were the contours of the biopsy needle and metal guide (Fig.13).

The direction and depth of the puncture were chosen based on the preoperative analysis of CT and/or MRI, where the size of the tumour, its relationship to nearly structures, and the extent of occlusion were determined. The direction of the puncture was established by rotating the device around the axis of the guide and controlled by the polyposition of fluoroscopy.



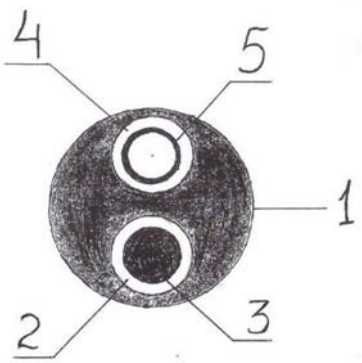


Fig. 6: Device for trephine biopsy of tumours of the head of the pancreas and the distal common bile ductbyE.B.Revazov–Ts.S.Khutiev

1 – device for trephine biopsy (frame); 2 – conductive channel; 3 – metal super-rigid guide type Lunderquist; 4 – internal opening of the puncture channel; 5 – biopsy needle; 6 – connector; 7 – distal end; 8 – projection; 9 – radio-opaque mark; a – angle to ensure operation of the device; b – angle of axial deviation of the biopsy needle.

To determine the technical aspects of performing trephine biopsy, we performed a continuous retrospective analysis from a database of 100 contrast-enhanced MRIs of the abdominal cavity in patients with a tumour of the head of the pancreas and biliary hypertension (Fig. 7). Studied the size and preferential localization of the tumour in relation to the hepaticocholedochus (HC), its relationship to the main pancreatic duct (MPD) and duodenum (DU). The age of the patients was 35-90 years, with average of 65±1,13. Men – 54 (54%), women – 46 (46%).

Sign	Minimum	Maximum	Average
Tumour size (mm)	11	89	35.4±1,53
Diameter of hepaticocholedochus (HC)(mm)	7.5	35	15,6±0,51
The length of the tumour narrowing of the HC(mm)	4	50	27±1,1
Hepaticocholedochus angle (degrees)	80	162	115,3±1,69
Diameter of the main pancreatic duct (MPD)(mm)	2	18	7,3±0,37
Distance from the level of the HC block to the level of the MPD block (mm)	1	63	11,9±1,02
Length from the proximal border of the HC block to the duodenum (mm)	14	52	30,8±0,91

Fig. 7: MRI-characteristics of a tumour of the head of the pancreas

Tumour size varied from 11 to 89mm, averaging 35,4±1,53 mm. According to the TNM system in stages T_1 – 4, T_2 – 60, T_3 – 32, T_4 – 4 patients. Signs of germination in the duodenum and MDP were noted in 18 (18%) patients; limited to invasion of parapancreatic tissue in 7 (7%) patients. Enlarged regional lymph nodes in 14 (14%) patients. Distant metastases were detected in 28 (28%) patients. Of them: T_1 – 2, T_2 – 10, T_3 – 15, T_4 – 1.

The diameter of the hepaticocholedochus (HC) ranged from 7,5 to 35 mm, on average – 15,6±0,51mm; the length of the tumour narrowing of the HC is from 4 to 50 mm, the average is 27±1,1mm. In 19 (19%) cases, an intact distal part of the common bile duct was identified extending from 5 to 36mm. The length from the proximal border of the HC block to the duodenum along the HC axis is 14 – 52mm, on average – 30,8±0,91mm.

The HC angle in the distal third was 80-160°, with an average of 115,3±1,69°. The magnitude of the angle depended on the predominant localization of the tumour, the degree of biliary hypertension and the associated elongation of the HC and its tortuosity. Currently, there is no clear understanding of the dependence of technical actions on a simple statement of the value of the angle HC. The opinion of an individual approach to this parameter and its further study remains.

The diameter of the main pancreatic duct (MPD) is from 2 to 18mm, on average – 7,3±0,37mm. The absence of pancreatic hypertension was noted in 14 (14%) patients, including 4 (4%) with a tumour size more than 40mm. 27 (27%) had MPD from 3,5 to 6mm and 57 (57%) had 6 mm or more. In 2 (2%) MPD was not possible to visualize due to the extensive of the tumour process in the pancreas.

The distance from the HC block level to the MPD block level ranged from 1 to 63mm, with an average of 11,9±1,02 mm. In 26 (26%) patients this distance is less than 7mm and in 13 (13%) of them the

MPD diameter is 6mm or more. Erosion of the internal contour HC in the area of the block was detected in 35 (35%), of which in 17 (17%) – like a "writing pen", in 9 (9%) – on the lateral side, in 9 (9%) – on the medal side; in 65 (65%) a "transverse block" is determined. There is no unambiguous connection between the predominant localization of the tumour and the size of HC contour usuration. Preferential location of the tumourabout HC: antemedial – 49 (49%), antegrade – 18 (18%), circular – 20 (20%), medial – 6 (6%), antelateral – 5 (5%), latero-antemedial – 2 (2%). In 67 (67%), the tumour thickness anterior to the HC lumen was more than 10 mm (Fig.8, 9, 10).

Analysis of the preferential localization of the tumour in relation to HC was one of the main ones for determining the technical feasibility and safety of performing transcholangiostomy biopsy. The thickness of the tumour anterior to the lumen of the HC of more than 10mm was examined in order to select the angle of β axial deviation of the biopsy needle in the original device for trephine biopsy. It was important that at the time of biopsy the needle penetrated the tumour tissue, but did not have the opportunity to exit into the free abdominal cavity.

Localization	Quantity (percentage)
Ante-medially	49 (49%)
Antegrade	18 (18%)
Circulary	20 (20%)
Medially	6 (6%)
Ante-lateral	5 (5%)
Latero-ante-medial	2 (2%)
The thickness of the tumour anterior to the lumen of the HC is more than 10mm	67 (67%)

Fig. 8: Preferential localization of the tumour in relation to hepaticocholedochus

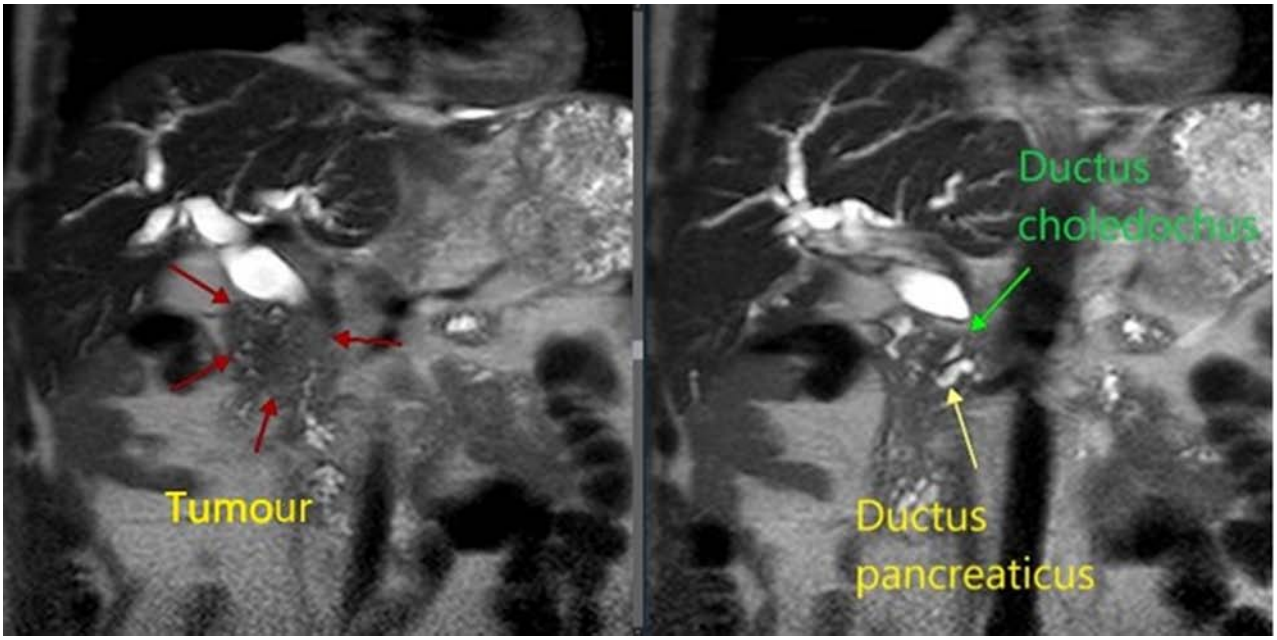


Fig. 9: Lateral localization of the tumour

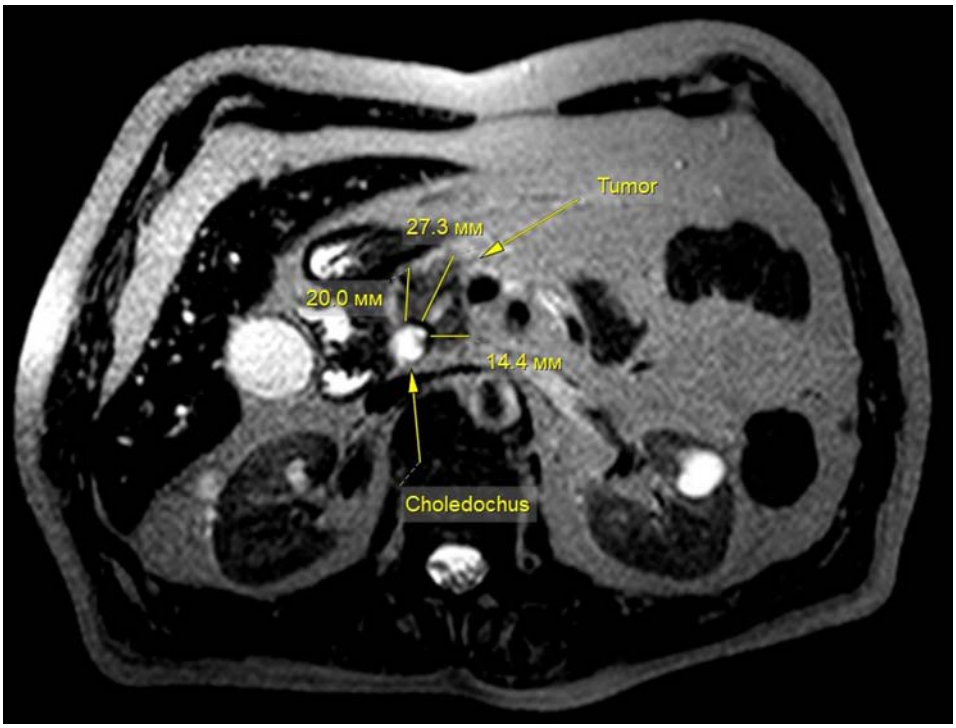


Fig. 10: Ante – medial localization of the tumour

As the result, we have identified a successful coincidence of the most common localization of the tumour of the head of the pancreas with the safest direction of transcholangiostomy biopsy – ante-medial and medial, which is effectively applicable in 77% of cases. Our chosen angle β of the axial deviation of the biopsy needle allows us to safely perform a biopsy in another 18% of cases (with antegradetumour growth), which is a total to 95%. The average distance from the proximal border of the tumour to the duodenum is up to 30,8±0,91 mm. Allows the use of an automatic biopsy system in most cases, including with a biopsy depth of 22 mm, avoiding the needle entering the duodenum with the risk of bleeding. If the tumour is small and there is a risk of damage to the duodenum or exit into the abdominal cavity, it is necessary to consider the possibility of aspiration-cutting biopsy in manual mode. Damage to the MPD can be reliable avoided in 87 (87%) of patients in any direction of puncture, because, taking into account the course of the MPD with HC, in 74 (74%)the MPD is located outside the puncture trajectory. In 13 (13%) patients, due to severe pancreatic hypertension, the probability of pancreatitis during MPD puncture is low. Cases of leakage of pancreatic juice through the puncture channel into the common bile duct will not have clinical significance.

The effectiveness of the method is explained by the fact that after passing the distal end of the original device (Fig. 6) along a metal guide through the tumour stenosis along the true lumen of the HC, we achieve tight contact of the internal opening of the puncture channel with the proximal border of the occlusion (Fig. 11). The correct choice of puncture direction necessarily ensures penetration into the tumour tissue with the collection of histological material. The combination of the biopsy needle and the metal guide ensures the safety of the intervention. The device is made of a double-lumen plastic tube, which determines its low cost. Ease of implementation makes the method accessible to most interventional radiologists.

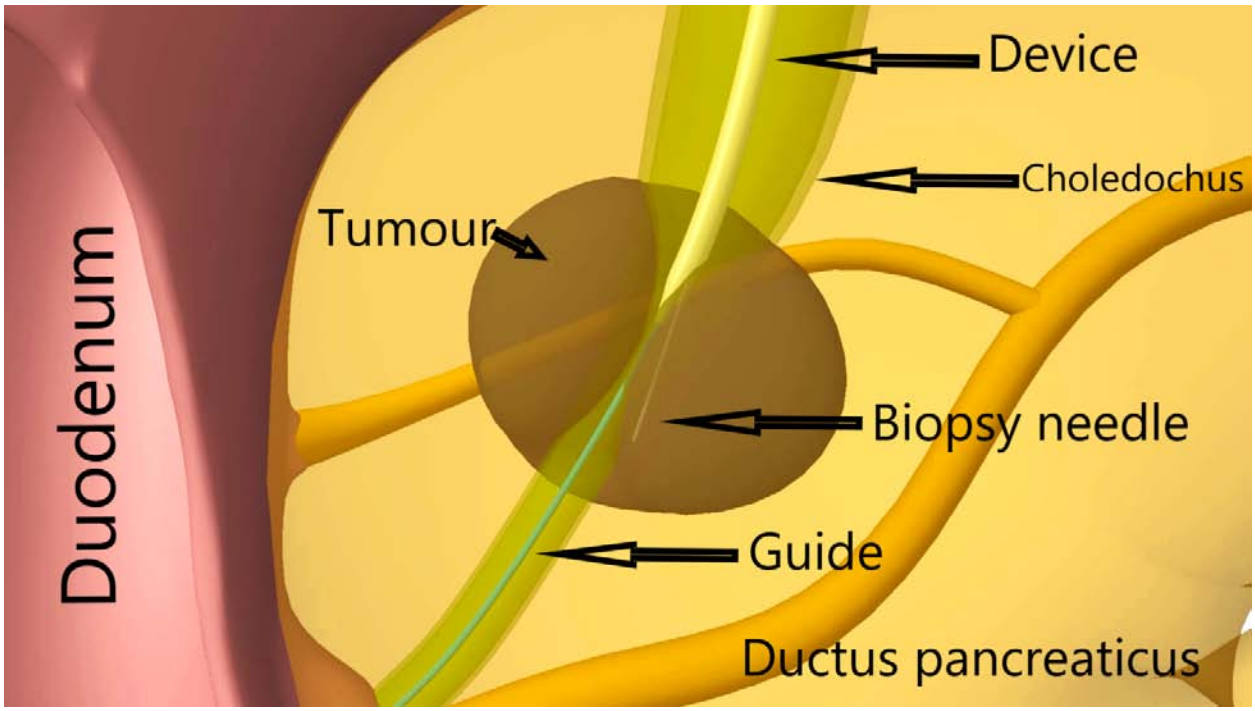


Fig. 11: Transcholangiostomy trephine biopsy of a tumour of the head of the pancreas by E.B.Revazov – Ts.S.Khutiev

As a result, the method we developed was used in 8 patients. Sufficient cytological and histological material was obtained in all cases. To take material, in two instances a Franzen 21G biopsy needle with a vacuum syringe was used, in 6 cases – a Bard Magnum 20G was used on the Bard Magnum automatic biopsy system. Cancer of the head of the pancreas was confirmed in 6 cases. In 4 hystologically and cytologically, in two instances – only cytologically. The absence of tumour tissue in the histological material in these patients is due to a biopsy along the edge of the tumour. Chronic pancreatitis was detected in 2 patients, confirmed in 1 case at the second stage of treatment. No complications were observed after using the trephine biopsy method we developed.

The issue of partial success in two cases, where we received only cytological confirmation of cancer in the absence of it in the histological material, we believe is due to insufficient development of the technique.

Figures 12-15 show the stages of transcholangiostomy trephine biopsy with external-internal drainage of the bile ducts and endoscopic papillsphincterotomy.

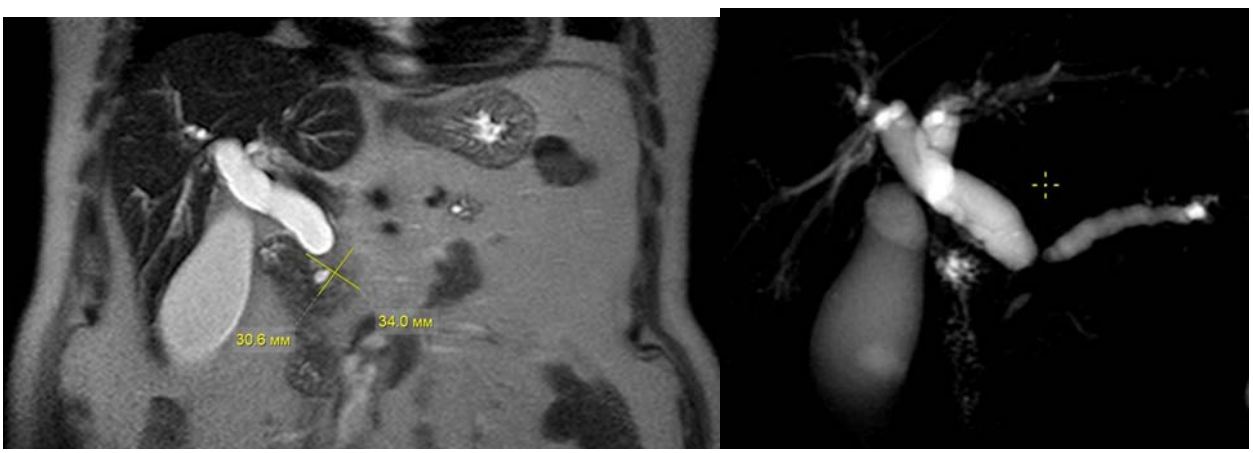


Fig. 12: Preoperative analysis of MRI of the abdominal cavity with MR-cholangiography

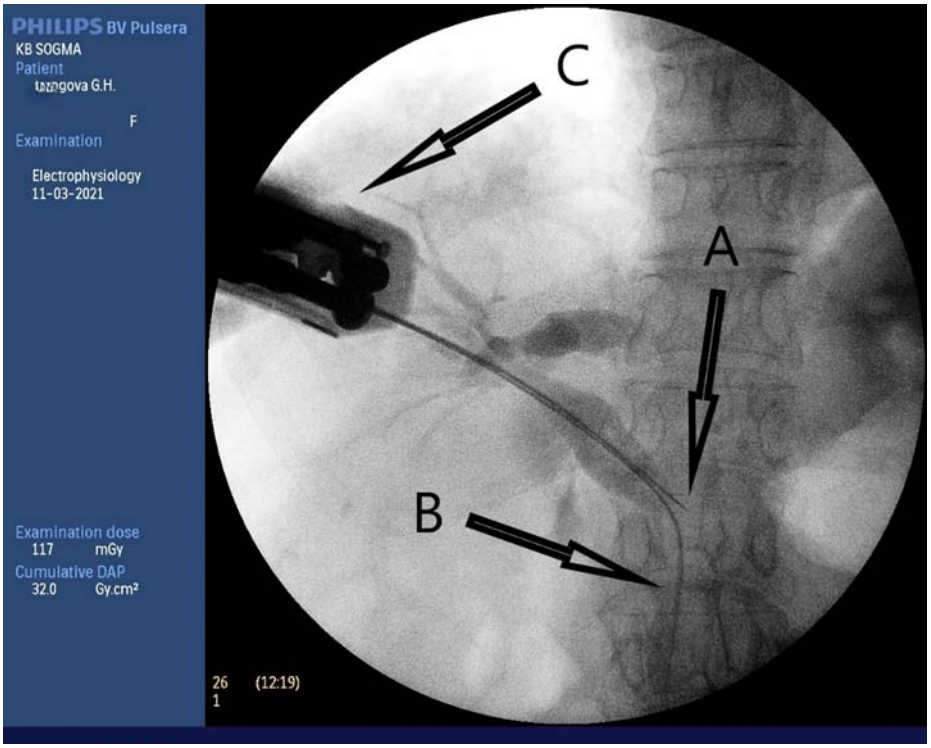


Fig. 13: Transcholangiostomy trephine biopsy of a tumour of the head of the pancreas (A – Biopsy needle; B – Super-rigid guide; C – biopsy gun.)

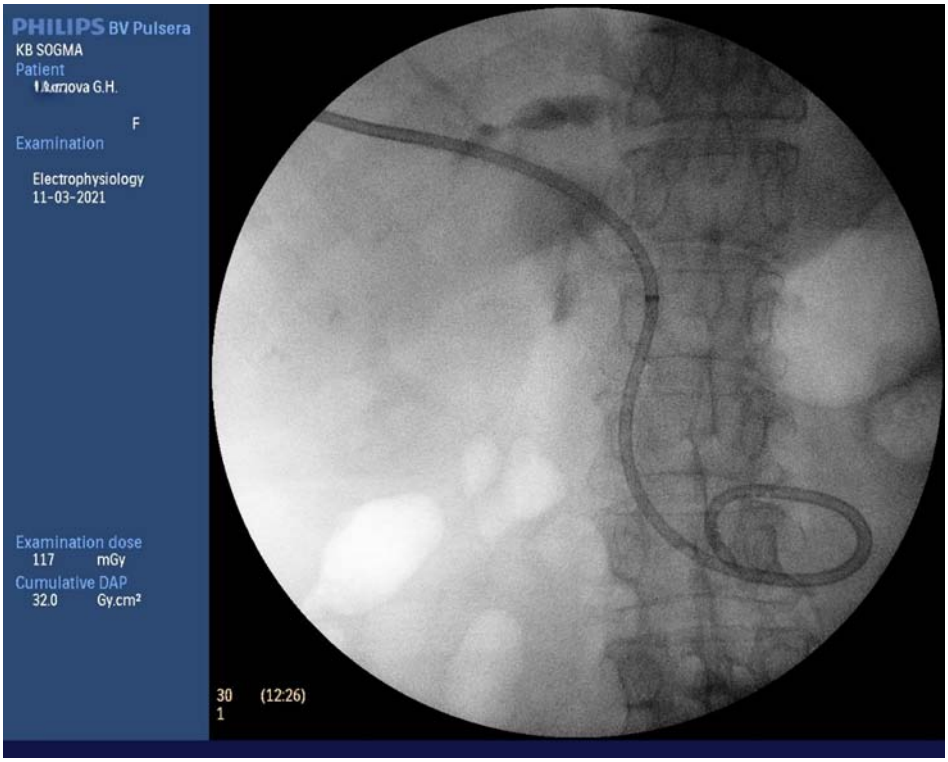


Fig. 14: External-internal drainage of the bile duct

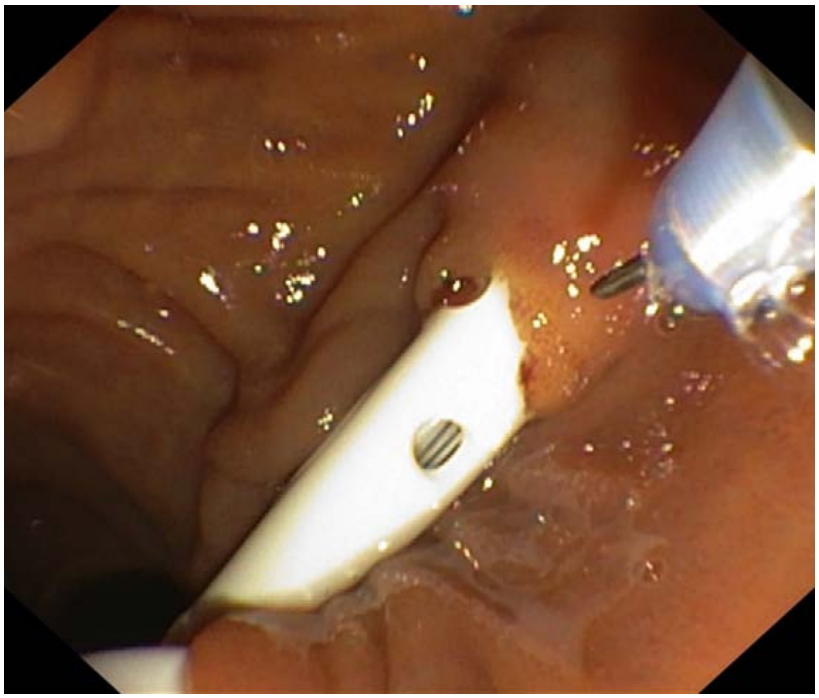


Fig.15: Endoscopic papillosphincterotomy.

V. Conclusion

The method of trephine biopsy of tumours of the head of the pancreas and the distal common bile duct (by E.B. Revazov – Ts.S. Khutiev) made it possible, within the framework of one combined minimally invasive surgical intervention, to perform internal drainage of the biliary tract with obtaining morphological verification in all 8 cases, in 6 of them – histological confirmation. No complications were observed. This distinguishes the method from fine-needle aspiration biopsy under EndoUS with a complication rate of 0,88-2% and obtaining predominantly cytological material. Transgastric trephine biopsy is currently not recommended due to the frequency of complications [31,32].

Preoperative MRI/CT analysis of the abdominal organs with contrast enhancement is necessary for safe and effective transcholangiostomy trephine biopsy of a tumour of the head of the pancreas and the distal common bile duct. These research methods provide sufficient information about the location, size of the tumour and its relationship to nearby anatomical structures. The main aspects are: the preferential localization of the tumour in relation to the HC, the distance from the proximal border of the tumour stricture to the duodenum along the true lumen of the hepaticocholedochus, the thickness of the tumour anterior to the HC.

The possibility of performingbiopsy with an automatic system (we consider it a priority due to the powerful mechanism) or semi-automatic needle is assessed – if the thickness of the tumour tissue along the puncture trajectory exceeds the length of the needle extension. If the thickness is insufficient, it is advisable to perform aspiration-cutting biopsy manually.

The first results of using the proposed method and device for trephine biopsy of tumours of the head of the pancreas and the distal common bile duct are scientifically substantiated and have proven effective. In our opinion, this makes our method a promising, reliable direction in solving the problem of morphological diagnosis of tumours of a given localization, complicated by obstructive jaundice. Further study on a large number of patients will reveal the true picture of the effectiveness and safety of the method. A priority method for preoperative testing will likely be identified. Criteria should be defined according to which preference will be given to aspiration and trephine biopsy.

Conflict of interest The authors declare no conflict of interest.

Compliance with ethical principles The authors confirm that they respect the rights of the people participated in the study, including obtaining informed consent when it is necessary, and the rules of treatment of animals when they are used in the study. Author Guidelines contains the detailed information.

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Memberships

Fellows/Associates of Medical Research Council

FMRC/AMRC Memberships

Introduction

FMRC/AMRC is the most prestigious membership of Global Journals accredited by Open Association of Research Society, U.S.A (OARS). The credentials of Fellow and Associate designations signify that the researcher has gained the knowledge of the fundamental and high-level concepts, and is a subject matter expert, proficient in an expertise course covering the professional code of conduct, and follows recognized standards of practice. The credentials are designated only to the researchers, scientists, and professionals that have been selected by a rigorous process by our Editorial Board and Management Board.

Associates of FMRC/AMRC are scientists and researchers from around the world are working on projects/researches that have huge potentials. Members support Global Journals' mission to advance technology for humanity and the profession.

FMRC

Fellow of Medical Research Council

FELLOW OF MEDICAL RESEARCH COUNCIL is the most prestigious membership of Global Journals. It is an award and membership granted to individuals that the Open Association of Research Society judges to have made a 'substantial contribution to the improvement of computer science, technology, and electronics engineering.

The primary objective is to recognize the leaders in research and scientific fields of the current era with a global perspective and to create a channel between them and other researchers for better exposure and knowledge sharing. Members are most eminent scientists, engineers, and technologists from all across the world. Fellows are elected for life through a peer review process on the basis of excellence in the respective domain. There is no limit on the number of new nominations made in any year. Each year, the Open Association of Research Society elect up to 12 new Fellow Members.

Benefits

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Get letter of appreciation

Global Journals sends a letter of appreciation of author to the Dean or CEO of the University or Company of which author is a part, signed by editor in chief or chief author.

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Get access to a closed network

A FMRC member gets access to a closed network of Tier 1 researchers and scientists with direct communication channel through our website. Fellows can reach out to other members or researchers directly. They should also be open to reaching out by other.

Career | Credibility | Exclusive | Reputation

Certificate

Certificate, LoR and Laser-Momento

Fellows receive a printed copy of a certificate signed by our Chief Author that may be used for academic purposes and a personal recommendation letter to the dean of member's university.

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Get honored title of membership

Fellows can use the honored title of membership. The “FMRC” is an honored title which is accorded to a person’s name viz. Dr. John E. Hall, Ph.D., FMRC or William Walldroff, M.S., FMRC.

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All the Fellow members of FMRC get a badge of "Leading Member of Global Journals" on the Research Community that distinguishes them from others. Additionally, the profile is also partially maintained by our team for better visibility and citation. All fellows get a dedicated page on the website with their biography.

Career | Credibility | Reputation

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Associate	Fellow	Research Group	Basic
$4800 **lifetime designation**	$6800 **lifetime designation**	$12500.00 **organizational**	APC **per article**
Certificate, LoR and Momento **2** discounted publishing/year **Gradation** of Research **10** research contacts/day **1 GB** Cloud Storage **GJ** Community Access	**Certificate,** LoR and Momento **Unlimited** discounted publishing/year **Gradation** of Research **Unlimited** research contacts/day **5 GB** Cloud Storage **Online Presense** Assistance **GJ** Community Access	**Certificates,** LoRs and Momentos **Unlimited** free publishing/year **Gradation** of Research **Unlimited** research contacts/day **Unlimited** Cloud Storage **Online Presense** Assistance **GJ** Community Access	**GJ** Community Access

Preferred Author Guidelines

We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

Alternatively, you can download our basic template from https://globaljournals.org/Template

Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at submit@globaljournals.org or get in touch with chiefeditor@globaljournals.org if they wish to send the abstract before submission.

Before and during Submission

Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

1. Authors must go through the complete author guideline and understand and *agree to Global Journals' ethics and code of conduct,* along with author responsibilities.
2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
3. Ensure corresponding author's email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s') names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

Declaration of Conflicts of Interest

It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

Policy on Plagiarism

Plagiarism is not acceptable in Global Journals submissions at all.

Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

Authors are solely responsible for all the plagiarism that is found. The author must not fabricate, falsify or plagiarize existing research data. The following, if copied, will be considered plagiarism:

- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures

- Printed material
- Graphic representations
- Computer programs
- Electronic material
- Any other original work

Authorship Policies

Global Journals follows the definition of authorship set up by the Open Association of Research Society, USA. According to its guidelines, authorship criteria must be based on:

1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

Declaration of funding sources

Global Journals is in partnership with various universities, laboratories, and other institutions worldwide in the research domain. Authors are requested to disclose their source of funding during every stage of their research, such as making analysis, performing laboratory operations, computing data, and using institutional resources, from writing an article to its submission. This will also help authors to get reimbursements by requesting an open access publication letter from Global Journals and submitting to the respective funding source.

Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

INDEX

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