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Diseases

Cancer, Ophthalmology & Pediatric

A Rare Cause of Cardiac Tamponade

Diagnosis of Autoimmune Encephalitis

Highlights

Regulation of Specific Cell Clusters

Increasing Immunity with Matily Herbal Drink

Discovering Thoughts, Inventing Future

VOLUME 20 ISSUE 8 VERSION 1.0

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Striational Muscle Antibody Positivity Heralding a Diagnosis of Autoimmune Encephalitis Associated with Epiglottic Squamous Cell Carcinoma: A Case Report

By Arun Swaminathan
University of Nebraska Medical Center

Abstract- A 59 yo woman presented to our emergency room with confusion, spells of loss of awareness over four weekswith malaise, weakness, gait difficulties, and 30 lb weight loss over one year. Brain imaging was unremarkable. EEGs revealed diffuse slowing, triphasic GPDs, and left temporal epileptiform discharges. Spinal fluid showed an elevated protein count. She received a working diagnosis of autoimmune encephalitis and received steroids and antiepileptic medications. She experienced an improvement in symptoms and went home. Follow up revealed elevated striational muscle antibodies and enhancement of spinal nerve roots suggesting an autoimmune neurological syndrome. She received intravenous immune globulin (IVIg) therapy and had periods of improvement followed by worsening a few months later with each dose of IVIg. She presented to the hospital a year with worsening dysphagia and an endoscopy showing an epiglottic mass. Pathology confirmed squamous cell carcinoma, and she received chemotherapy and radiation. We wish to share this rare case of autoimmune encephalitis presenting with only striational antibodies as a heralding sign of a tumor. We postulate that, in the correct context, the presence of striational antibodies alone, despite low titers, may support a diagnosis of autoimmune encephalitis from underlying malignancy.

Keywords: *epilepsy, autoimmune encephalitis, striational antibodies.*

GJMR-F Classification: *NLMC Code: WP 460*

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Striational Muscle Antibody Positivity Heralding a Diagnosis of Autoimmune Encephalitis Associated with Epiglottic Squamous Cell Carcinoma: A Case Report

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Keywords: epilepsy, autoimmune encephalitis, striational antibodies.

Abbreviations

EEG – electroencephalogram
GPDs – Generalized Periodic Discharges
GRDA – Generalized Rhythmic Delta Activity
IVIg – Intravenous Immune Globulin
CSF – Cerebrospinal Fluid
ENT – Ear Nose Throat doctors –otorhinolaryngologists

I. Case Presentation

A 59 yo right-handed woman was brought into our emergency room by her family with multiple complaints. She had intermittent spells of confusion lasting for a few minutes with associated word-finding difficulty and staring as well, which occurred 2-3 times a week, on average. She also complained of generalized weakness and fatigue, which had been slowly worsening over the last year. She also reported difficulty with walking and endorsed back pain in addition to diffuse muscle weakness. She had a remote history of breast cancer 18 years ago, for which she had undergone resection and chemotherapy.

MRI imaging of her brain was unremarkable. Video EEG testing revealed diffuse polymorphic slowing with intermittent generalized rhythmic delta activity (GRDA) in addition to triphasic generalized periodic discharges (GPDs) and occasional left temporal epileptiform discharges (Figures 1, 2, 3). These findings were felt to be suggestive of a diffuse cerebral dysfunction and new-onset epileptogenic potential as well. Spinal fluid analysis revealed elevated protein level of 61 mg/dL (normal range – 15-45 mg/dL). CSF cytology was negative for malignancy, and there were no unique oligoclonal bands in the CSF either. CAT scans of her body did not reveal a malignancy. ESR and CRP were elevated at 84 and 18, respectively. We diagnosed her with possible autoimmune encephalitis, given her clinical context with the EEG and CSF findings. She was treated with intravenous steroid therapy and antiepileptic medications (levetiracetam and lacosamide) and returned to normal mental baseline in a few days. She was discharged home and scheduled for outpatient follow up.

Further workup revealed the presence of striational muscle antibodies at a titer of 1:480 in the blood. CSF autoimmune panel was negative. Other auto-antibodies were negative as well. MRI imaging of her spine showed subtle enhancement of her spinal nerve roots, suggestive of a possible inflammatory process. EMG/NCV testing with repetitive nerve stimulation revealed a chronic ulnar neuropathy but no other findings. Imaging and autoimmune antibody evaluation did not capture any abnormalities.

As her symptoms returned a few weeks later, we decided to initiate therapy with intravenous immune globulin (IVIg) for a probable autoimmune neurological syndrome – autoimmune encephalitis without any features of peripheral neuromuscular hyperexcitability. She received three courses of IVIg over the next 1 year

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and had significant improvement in her symptoms, both mental (impaired awareness, confusion) and physical (weakness, gait difficulty). She also did not have any noticeable seizures and remained on levetiracetam and lacosamide therapy during this time.

One year after her first presentation, she presented to her PCP with complaints of worsening dysphagia. She was referred to the ENT doctors for evaluation and underwent an endoscopy, which discovered an epiglottic mass of about 1 cm diameter. We performed a biopsy and histopathology confirmed diagnosis of squamous cell carcinoma of her epiglottis (Figures 4, 5). Her 40-pack year smoking habit was contributory to her malignancy.

She saw oncologists and received chemotherapy and radiation. She remains stable, continues to receive antiepileptic medications and immune therapy for her symptoms, and follows up with us in the epilepsy clinic.

II. Discussion

Autoimmune encephalitis is an uncommon presentation of malignancy. Presenting symptoms are often diverse, including but not limited to, memory loss, personality changes, seizures, cognitive impairment, and overall loss of function[1]. The presentation is often subacute and subtle, with symptoms occurring insidiously over weeks to months before family members or friends note frank presentation. Steroid therapy is often therapeutic, produces dramatic improvement, and frequently serves as a diagnostic and therapeutic intervention in such patients. Our patient's symptoms, while consistent with many of the previously described features of autoimmune encephalitis, was still nonspecific.

Isolated striational antibody positivity is not a classic finding in patients with autoimmune encephalitis. The antibody is typically associated with peripheral hyperexcitability syndromes, like Isaac's or Morvan's syndromes or myasthenia gravis. It is seen in patients with autoimmune encephalitis in coexistence with neuromuscular syndromes, especially with elevated titers of other autoantibodies[2, 3, 4]. Titers of striational autoantibodies are also felt to play a role, with lower titers usually seen to represent evidence of autoimmunity, rather than the presence of an underlying malignancy, especially with the absence of other autoantibodies[5]. A striational antibody titer of at least 1:7680 is reportedly suggestive of an underlying malignancy, especially in conjunction with antibodies like VGKC complex, GAD 65, or others. Prior malignancy is causative of a low titer of striational antibodies, rather than a current active malignancy[5]. Our patient had a relatively low titer of striational antibodies at 1:480, which, coupled with her previous diagnosis of breast cancer, did not initially support the probability of a newer malignancy. Absence of a amalignancy on the chest and abdominal imaging further suggested a lower possibility of a tumor, since lung and thymus tumors are most commonly associated with paraneoplastic syndromes[3, 5, 6]. EMG/NCV testing ruled out peripheral hyperexcitability as well, making autoimmune encephalitis less likely[3, 4].

We approached the diagnostic dilemma and treatment plans for patients with a presumptive diagnosis of possible autoimmune encephalitis. Our patient had subacute onset of symptoms inclusive of encephalopathy and confusion, new-onset seizures, and a reasonable exclusion of other causes, meeting all three criteria for a diagnosis of possible autoimmune encephalitis (Table 1) [7]. We decided to pursue empirical therapy with intravenous steroids due to the potential benefits and relatively low probability of risk in this clinical context. Our patient responded to steroid therapy, which seemed to strengthen our presumptive diagnosis of autoimmune encephalitis. We do concede that other conditions, like lymphomas, would also respond to steroid therapy. Still, we were reasonably confident that such diagnoses could be excluded based on the negative results seen on our extensive testing. Immune globulin therapy represents the standard of care, and she had responses to multiple courses of IVIg followed by a slow progression of symptoms over weeks-months after treatment, supporting our working diagnosis of autoimmune encephalitis. Her EEG tests did show diffuse slowing with triphasic waves and left temporal epileptiform discharges – findings that would favor diffuse cerebral dysfunction and new-onset seizures. While these findings were not specific for autoimmune encephalitis, they did add supportive evidence to the diagnosis of possible autoimmune encephalitis.

Table 1: Diagnostic criteria for possible autoimmune encephalitis[7] –

Diagnosis can be made when all three of the following criteria have been met:
1) Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2) At least one of the following: • New focal CNS findings • Seizures not explained by a previously known seizure disorder • CSF pleocytosis (white blood cell count of more than five cells per mm^3) • MRI features suggestive of encephalitis
3) Reasonable exclusion of alternative causes

Epiglottic tumors are not commonly associated with autoimmune neurological syndromes, and our workup did not reveal such a tumor during our initial round of testing, including whole-body PET scans. Lung cancers and thymomas are most commonly associated with autoimmune encephalitis and striational antibody-related paraneoplastic neurological syndromes[6], and we were able to exclude these relatively common conditions with our imaging tests, especially given her history of smoking.

In summary, we can state that our patient represents a rare case of autoimmune encephalitis presenting with subacute symptoms, heralded by a diagnosis of positive striational autoantibodies, in association with epiglottic cancer. All these findings constitute a rare constellation of results and symptoms and make this patient's case worthy of publication and scientific study.

III. Conclusions

Autoimmune encephalitis must be considered in any patients presenting with subacute cerebral dysfunction and new-onset seizures. Extensive cerebral and whole-body imaging and additional testing are essential to confirm the diagnosis and exclude other conditions as well. We recommend empirical steroid or immune therapy at the earliest due to the potential for improvement with minimal potential risk. Consultation by an expert neurologist, epileptologist, oncologist, or rheumatologist is also advised at the earliest, especially if the patient is unstable or rapidly declining. Serial imaging and surveillance are often required before the diagnosis is confirmed and may take months to years to achieve. Empirical immune therapy must be considered with correct clinical and serological guidance and should probably be performed under expert consultation only.

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Permissions and guidelines

The patient and her family consented to the publication of this case report. All scientific and ethical guidelines were followed during the compiling and publication of this report and this publicationis consistent with those accepted guidelines.

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Legends

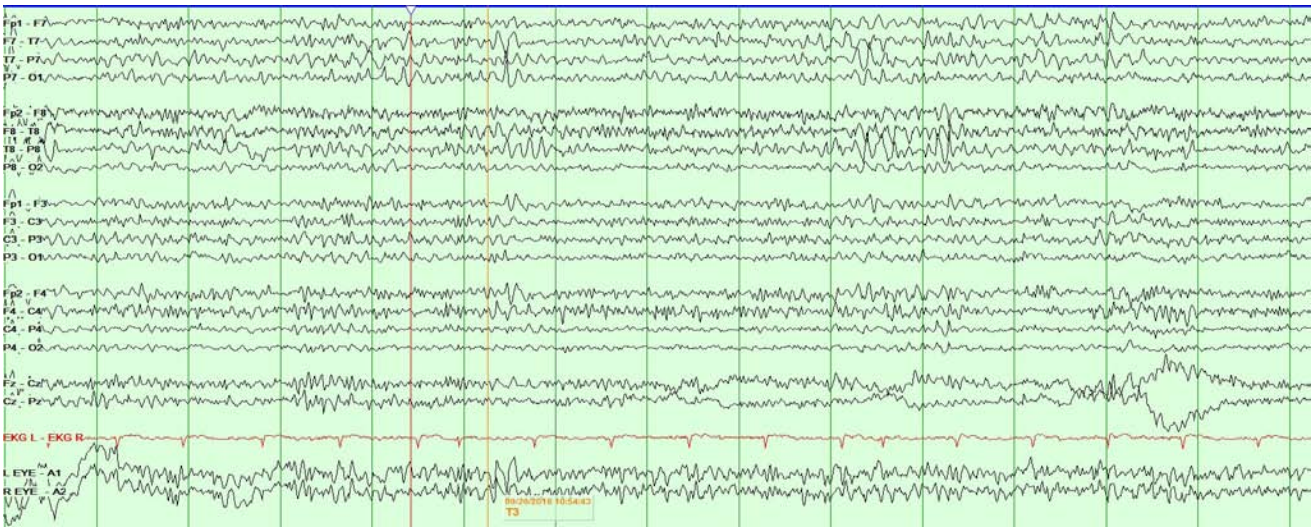


Figure 1: EEG with double banana montage showing a left temporal epileptiform discharge

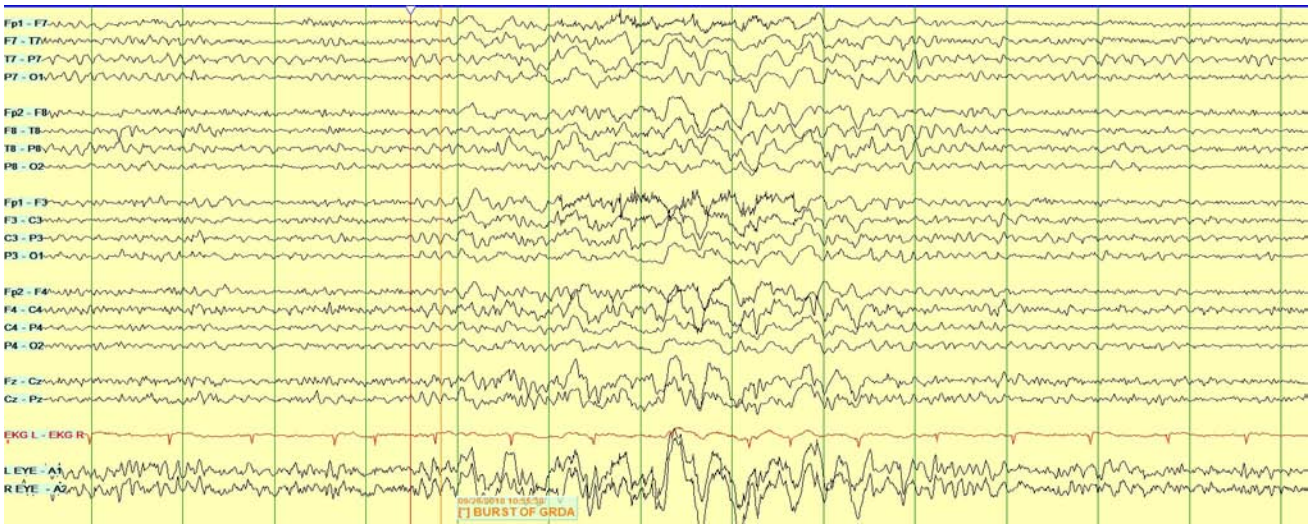


Figure 2: EEG with double banana montage showing generalized rhythmic delta activity – GRDA – with diffuse polymorphic slowing

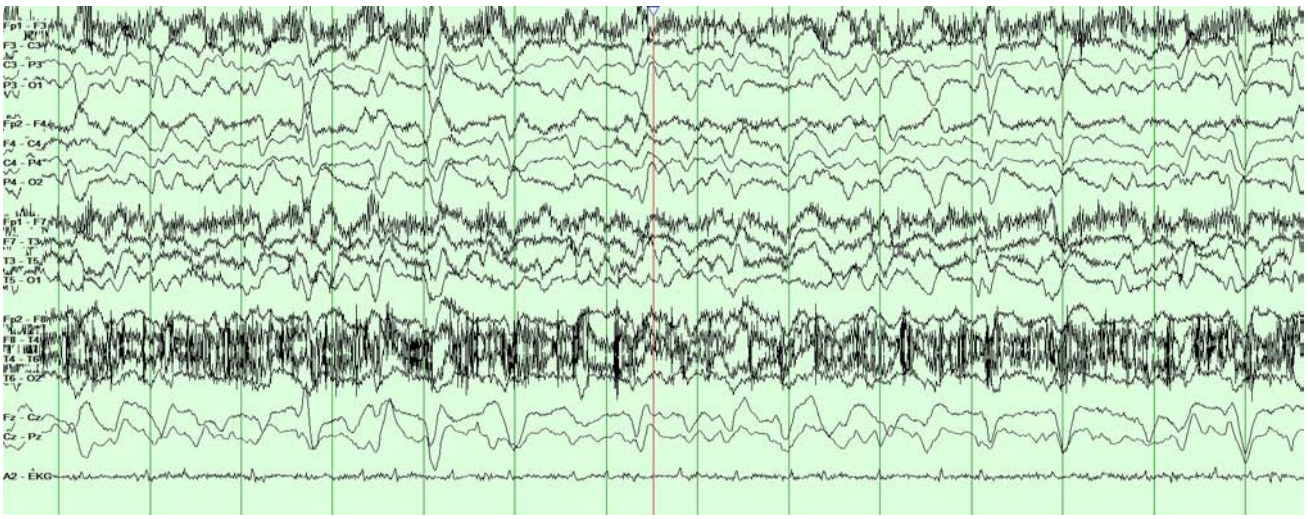
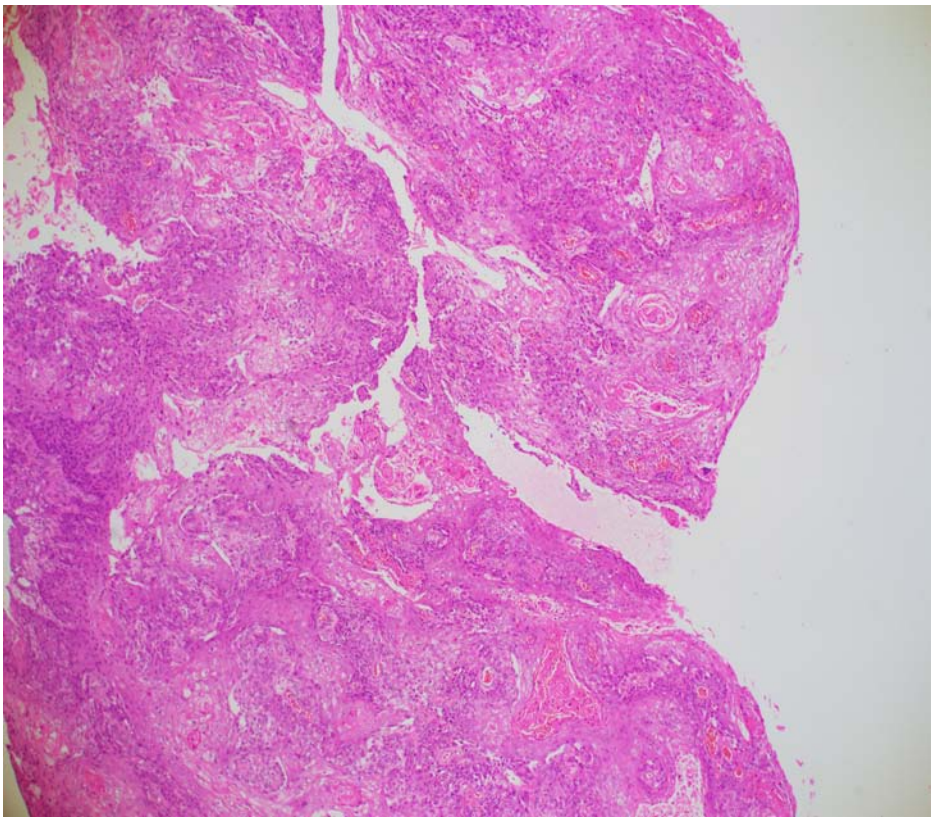
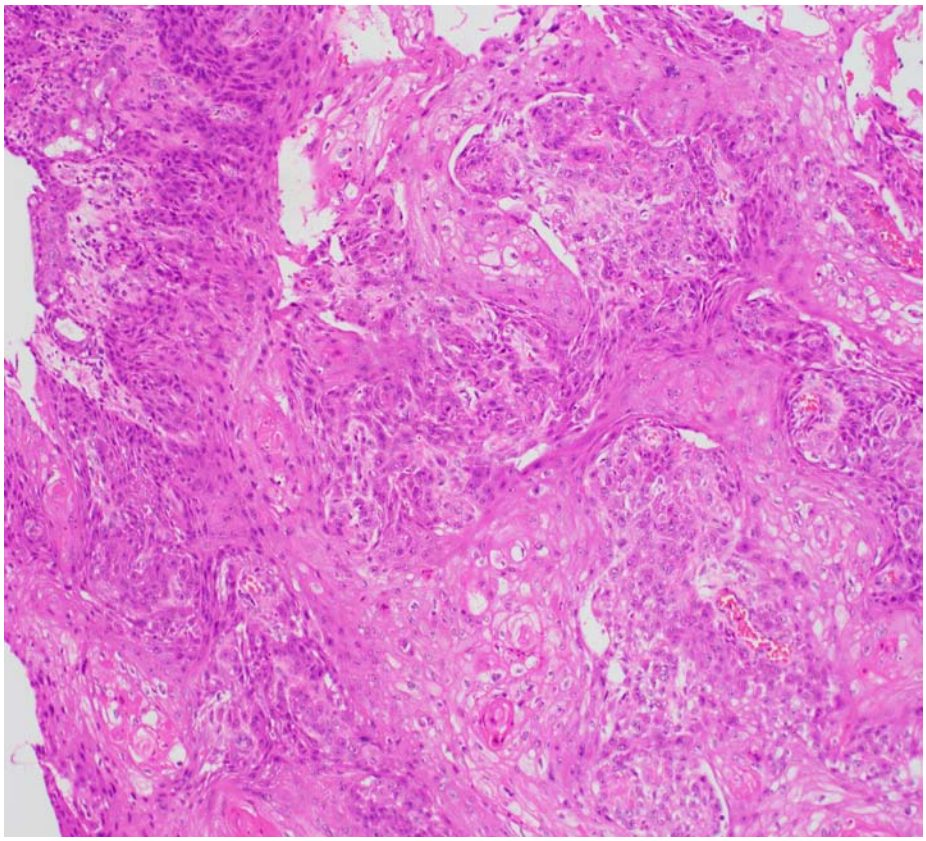


Figure 3: EEG with double banana montage showing generalized periodic discharges – GPDs – with triphasic morphology at 1-2 Hz





Figures 4 & 5: Histopathology of epiglotticlesion - Invasive squamous cell carcinoma of the epiglottis with infiltrative growth, keratinization, moderate nuclear pleomorphism and scattered mitotic figures. Fig 4 (H&E 10X) & Fig 5 (H&E 20X)

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Brevundimonas Vesicularis: Unusual Cause of Bacteraemia in Otherwise Healthy 8 Months Old Premature Child: Case Report

By Anood Al Rawahi & Hilal Al Hashami

Abstract- *Brevundimonas vesicularis,* a non-fermenting gram-negative bacterium, has rarely been diagnosed as a cause of infection in an otherwise healthy child. In this report, we describe *Brevundimonas vesicularis* bacteremia, in an 8 months old healthy girl who was treated successfully with intravenous piperacillin-tazobactam.

GJMR-F Classification: *NLMC Code: QW 50*

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I. Introduction

Gram-negative bacteremia (GNB) is a common clinical encounter in children with a history of recurrent hospital admission or immunocompromised children. Growth of GNB from a sterile site should be considered carefully even in an otherwise healthy children with no predisposing risk factors for such infection. We present a case of *Brevundimonas vesicularis* bacteremia in otherwise healthy eight months old premature baby girl with a history of prolonged NICU admission without any prematurity complications.

II. Case Presentation

Eight months old twin one of monochorionic diamniotic twins with corrected age of 6 months, born at 31 weeks of gestation via elective caesarian section required neonatal intensive care unit (NICU) admission for 20 days due to low birth weight. She remained asymptomatic after discharge from NICU. She brought by her parents to the emergency department with a history of cough, fever and increase work of breathing for a one-week duration. Cough is wet, with no post-tussive vomiting. No cyanosis or episodes of apnea. On examination, she was sick looking, febrile with temperature 38.6 C, respiratory rate 52 breath per minute, heart rate 150 beats per minute. The chest examination revealed a wheezy chest. Her investigations showed: total white blood cells WBC: 15.3x 10^9 cells/L neutrophils 12.1x 10^9/L, lymphocytes 2.6x 10^9/L, monocytes 0.4 x 10^9/L, eosinophils 0.1 x 10^9/L, basophils 0.1 x 10^9/L. blood gas: pH = 7.41, pCO2 = 38mmHg, pO2 = 89.9mmHg, bicarbonate = 24mmol/L. The respiratory viral panel came positive for the respiratory syncytial virus (RSV). Peripheral blood culture collected along with catheterized urine culture. Chest X-ray showed: right-sided infiltrate (figure1). The initial clinical impression was chest infection based on tachypnea, chest x-ray findings, and high total white blood cells. She was admitted for intravenous antibiotics.

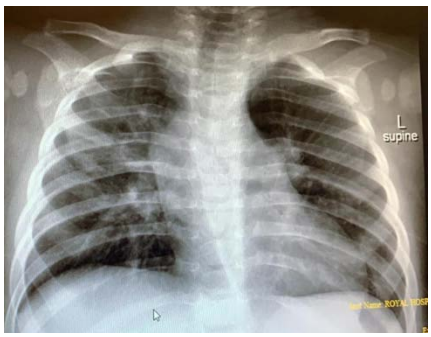

Figure 1: Chest x-ray of the child

She was started empirically on intravenous Augmentin 30 mg three times a day. She required frequent suctioning on the first day of admission along with nasogastric tube (NGT) feeding of 75ml every 2 hours along with PRN salbutamol nebulization as she continued to have a wheezy chest. By the second day of admission, she continued to spike a fever and had reduced activities despite improvement in her respiratory status.

On the 3rd day of admission, the blood culture flagged positive for gram-negative bacilli sensitive to piperacillin + tazobactam, gentamycin, and cefepime, resistant to ciprofloxacin and ceftazidime. Based on the sensitivity report; augmentin changed to intravenous

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piperacillin-tazobactam 0.95 grams 8 hourly. Two days later, the final identification of the gram-negative bacilli reported as *Brevundimonas Vesicularis*. Clinically, the patient improved after the 2nd day of intravenous piperacillin-tazobactam. She became a febrile, her activities improved, and her general condition also improved. She did not show any signs of meningitis, urine analysis and culture were negative. Repeated blood culture 48 hours after starting her on piperacillin-tazobactam came negative for bacterial growth. As this organism is more common in immunocompromised patients, the child was investigated for immunodeficiency. The following investigations were done: immunoglobulin IgG 7.9 g/L (2.02 – 9.5), immunoglobulin IgA 0.32g/L (.08 - .91), immunoglobulin IgM 0.83 g/L (.17-1.5). Lymphocytes subset analysis panel including; Total lymphocytes 5.73x 10^9, T-cell (CD3+) = 5.01 x 10^9, B-cell (CD19+) = 1.26 x 10^9, T-helper (CD3+/CD4+) = 3.94 x 10^9, T-cytotoxic (CD3+/CD8+) = 1.01 x 10^9, CD4:CD8 ratio = 3.90 x 10^9, NK-cells (CD3-/CD56+) = 0.26 x 10^9. All her immunological investigations were within normal and were not suggestive of primary immunodeficiency.

She discharged after completing ten days of intravenous antibiotics. On subsequent out-patient follow-up, she remains asymptomatic and is gaining weight and gaining her milestones according to her chronological age.

III. Discussion

The *Brevundimonas* are a genus of proteobacteria, gram-negative, non-fermenting, aerobic bacilli. Oxidase and catalase-positive. Two species of *Brevundimonas* classified under the genus *pseudomonas* then it has been re-classified by Seger et al. as *Brevundimonas vesicularis* and *Brevundimonas diminuta*[1]. There have been many cases reports of *Brevundimonas* infection isolated from different sites such as skin and soft tissues, urinary tract infections, liver abscess, meningitis, and peritonitis. The predisposing factors of *Brevundimonas* infection are not well known. Most of the infection occurs in immunocompromised patients such as those with prolonging steroid therapy, systemic lupus erythematosus (SLE), end-stage renal disease, and malignancy.[2] This organism has also been isolated from environmental samples such as soil, tap water, and hospital instruments.[3]

Previous case reports of the same organism showed a variety of drug susceptibility. Although it was not used frequently to treat this organism, most of the cases reported showed no resistance to cotrimaxazole, which also observed in our case. Piperacillin+ tazobactam is the most common medication which used in most of the reported cases. Shang et al. observed that the organism was sensitive to aminopenicillins, penicillins, cephalosporins, carbapenems, and it was resistant to aztreonam, ceftazidime, and ciprofloxacin[2].

Our reported case was sensitive to piperacillin + tazobactam, gentamycin, and cefepime. It was resistant to ciprofloxacin and ceftazidime. The child improved with piperacillin + tazobactam treatment course for a total of 10 days' duration with no complications. Karadag et al, reported in his study of a 29-week-old neonate who developed early neonatal sepsis due to the same organism complicated by persistent meningitis and lymphadenopathy.[4]

The infection caused by *Brevundimonas* can have different presentations. One reported case of *Brevundimonas* septicemia complicated by bilateral pneumothorax and empyema in an eight-months-old infant who presented with fever, rapid breathing, and poor oral intake required chest tube insertion, treated successfully with Cefoperazone and levofloxacin then discharged after two weeks of treatment.[5] Another case reported in an immunocompetent young male, presented with liver abscess required drainage in addition to antimicrobial therapy of ceftriaxone followed by ampicillin/sulbactam.[6] A rare presentation of septic arthritis of shoulder joint in a previously healthy toddler witch managed successfully with cefuroxime antibiotic.[7]

The present case report demonstrates the importance of diagnosing *Brevundimonas* bacteremia, particularly in otherwise a healthy child with no predisposing risk factors if the whole clinical picture cannot be explained by the viral infection.

IV. In Conclusion

Brevundimonas causes serious infection rather than just be considered as a contamination in high-risk setting. Once it is isolated from a sterile site, it should be taken seriously and appropriate antibiotic therapy should be started. Early treatment with follow up culture is the kay to prevent morbidity and mortality related to this infection.

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Regulation of Specific Cell Clusters in TCR-T Cells Responding to Differential Expression of Tumor PD-L1

By Renpeng Ding, Shang Liu, Huanyi Chen, Bin Kang, Radoje Drmanac, Ying Gu, Xuan Dong & Qianqian Gao

University of Chinese Academy of Sciences

Abstract- PD-L1 signaling is essential in regulating T cell function and keeping the balance of tumor microenvironment, but its role in modifying TCR-T cell cytotoxicity remains unknown. MART-1-specific TCR-T cells (TCR-T_{MART-1}) were stimulated by MEL-526 tumor cells expressing different proportions of PD-L1 and used to perform cytotoxicity assays and single-cell RNA sequencing. Percentage changes of different specific cell clusters were analyzed. The percentage of cluster HLA-$DR^+CD38^+CD8^+$ was upregulated after antigen stimulation, and tumor PD-L1 modified TCR-T cell function through downregulating the percentages of HLA-$DR^+CD28^+CD8^+$ and HLA-$DR^+CD38^+CD8^+$ subsets which were higher in TCR-T_{MART-1} than in T_{null}.

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I. Introduction

PD-L1 (programmed death-ligand 1) takes participation in regulating T cell-mediated immune responses for tumor evasion from the immune system, thus promotes cancer development and progression [1]. PD-L1 is also known as CD274 or B7-H1 and is one ligand for PD-1 (programmed death- 1). PD-L1 is wildly expressed on tumor cells of various types of malignancies, including melanoma, while PD-1 is highly expressed in tumor-infiltrating lymphocytes [2]. PD-L1 interacts with PD-1 resulting in T cell dysfunction and exhaustion, but the effect of tumor PD-L1 expression on TCR-T (T-cell receptor-engineered T cells) cell function has not been comprehensively studied. TCR-T cell therapy has great potential in mitigating tumor development, especially for solid tumors. The number of clinical trials with TCR-T cell therapy is increasing each year, and among them, the most targeted cancer type is melanoma [3]. Therefore, it's important to investigate how tumor PD-L1 expression affects TCR-T cell functionality.

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Author ν: Lead Contact

In our study, single-cell mRNA sequencing (scRNA-seq) was performed to investigate MART-1-specific TCR-T cells responding to different proportions of PD-$L1^+$melanoma cells. Distribution of specific cell clusters such as HLA-$DR^+CD28^+CD8^+$ and HLA$DR^+CD38^+CD8^+$ was modified with increasing ratio of tumor PD-L1.

II. Results

a) TCR-T_{MART-1}killed MEL-526 tumor cells efficiently at E:T ratio of 1:1

HLA-A*0201/MART-1-specific TCR sequence was obtained from T cells after stimulation with MART-1 (aa27-35, LAGIGILTV) peptide (data unpublished) and designed as TCR_{MART-1} (Fig. 1). To avoid mispairing with endogenous TCR [4], TCR_{MART-1} α and β chains were fused with the constant region of murine TCR and synthesized before cloned into the lentiviral vector (Fig. 1). After transfection of TCRMART-1 lentivirus, $CD8^+$T cells expressed TCR_{MART-1} or not were designed as TCR-T_{MART-1} and T_{null}, respectively. TCR-T_{MART-1} and T_{null} cells were stimulated with peptide-loaded MEL-526 melanoma cells at different E:T ratios (1:1, 1:2, and 1:4. Fig. 2) to assess the killing capacity. Compared to T_{null}, TCR-T_{MART-1} killed tumor cells more efficiently, especially at E:T ratio of 1:1 (Fig. 2).

b) Regulation of specific T cell clusters responding to different proportions of PD-L1+ tumor cells

To verify the effect of tumor PD-L1 expression on TCR-T cell function, MEL-526 cells expressing low, intermediate, and high levels of PD-L1 (data unpublished, designed as PD-$L1_{low}$, PD-$L1_{int}$, and PD-$L1_{high}$, respectively and PD-L1 expression ratio was about 3%, 50%, 100%) were incubated with TCR-T_{MART-1} (50% $TCR_{MART-1}{}^+$). The percentage of specific $CD8^+$ T cell clusters, including $CX3CR^+$, HLA-DR^+, HLA-DR^+CD28^+, and HLA-DR^+CD38^+, were analyzed in T cells (Fig. 3). The percentages of $CX3CR^+$, HLA-DR^+, and HLADR^+CD28^+ clusters were decreased, while the proportion of HLA-DR^+CD38^+subsetwas increased after antigen stimulation (Fig. 3). Furthermore, the ratios of HLA-DR^+CD28^+ and HLA-DR^+CD38^+subpopulations were reduced by the increasing proportion of tumor PD-L1 (Fig. 3).

When T cells were further divided into T_{null} and TCR-T_{MART-1}, the percentages of HLA-DR^+CD28^+ and HLA-DR^+CD38^+ clusters were higher in TCR-T_{MART-1} than in T_{null} (Fig. 4). Consistently, the percentages of HLA-DR^+CD28^+ and HLA-DR^+CD38^+ clusters in both T_{null} and TCR-T_{MART-1} was downregulated with the increasing proportion of tumor PD-L1 (Fig. 4).

c) $CX3CR^+CD8^+$ cluster was characterized by GZMA expression

Differentially expressed genes (DEGs) were analyzed in these specific clusters. Except for CX3CR1, the expression of cytotoxic genes GZMA and NKG7 and chemokine CCL5 was upregulated in the CX3CR+ cluster, while the expression of *IL2RA, XCL1,* and *GZMB* were downregulated compared to $CX3CR^-$ cells (Fig. 5A). After gene oncology (GO) analysis, T cell activation and cell-cell adhesion related signaling were enriched in the CX3CR+ cluster (Fig. 5B).

d) HLA-DR^+CD8^+ cluster was characterized by IL32 and GZMA expression

In addition to *GZMA* and *CCL5* expression, which was upregulated in the $CX3CR^+$ cluster as well, the expression of cytokine *IL32* was increased in the HLA-DR^+CD8^+ cluster (Fig. 6A). Endocytic vesicle membrane signaling was enriched in the HLA-DR^+CD8^+subset (Fig. 6B).

e) HLA-$DR^+CD28^+CD8^+$ cluster was characterized by CD52 expression

The expression of *CD52* was increased in addition to *CD28* in the HLA-$DR^+CD28^+CD8^+$ cluster (Fig. 7A). Though not so dramatic as that of *CD52*, the expression of *CCL5* and *JAK1*, which are essential for cytokine signaling, was upregulated as well. Leukocyte activation related pathways were enriched in this cluster (Fig. 7B), which was much similar to that of the $CX3CR^+CD8^+$population (Fig. 5B).

f) HLA-$DR^+CD38^+CD8^+$ cluster was characterized by GZMB expression

One characteristic of the HLA-$DR^+CD38^+CD8^+$ cluster was the upregulated expression of *GZMB* (Fig. 8A), which plays a critical role in T cell cytotoxicity. Metabolic process-related signaling pathways were enriched (Fig. 8B), indicating the active status of this cluster.

III. Discussion

CX3CR1 expression on $CD8^+$ T cells is associated with cytotoxic capability [5, 6]. Consistently, DEG analysis of $CX3CR^+CD8^+$ cluster was characterized by upregulated expression of cytotoxic genes *GZMA* and *NKG7* (Fig. 5A) and T cell activation signaling was top enriched in this cluster (Fig. 5B). But the percentage of $CX3CR^+CD8^+$ cluster was quite low in T cell populations (Fig. 3, Fig. 4), indicating a weak role of this cluster under the circumstances. HLA-DR^+CD8^+ T cells are considered activated cytotoxic T lymphocytes [7], and HLA-$DR^+CD28^+CD8^+$ T cells showed telomerase activity with proliferative potential [8]. The percentages of clusters $CX3CR^+CD8^+$, HLA-DR^+CD8^+, and HLA-$DR^+CD28^+CD8^+$ were downregulated, in contrast, the proportion of HLA-$DR^+CD38^+CD8^+$ cluster which was defined as activated T cells during the acute phase of viral infections [9], was upregulated after antigen stimulation compared to that in unstimulated Ctrl group (Fig. 3). The results indicated various changes inproportions of different cell subsets, though they might have similar functions. On another aspect, the percentages of clusters HLA-$DR^+CD28^+CD8^+$ and HLA-$DR^+CD38^+CD8^+$ were decreased with the increased proportion of PD-$L1^+$ tumor cells (Fig. 3), implying the inhibition of tumor PD-L1 on the percentages of clusters HLA-$DR^+CD28^+CD8^+$ and HLA-$DR^+CD38^+CD8^+$ might result in the damage on TCR-T cell cytotoxicity (unpublished data).

The percentages of clusters HLA-$DR^+CD28^+CD8^+$ and HLA-$DR^+CD38^+CD8^+$ were higher in TCR-T_{MART-1} than in T_{null}, while there was no significant change in the distribution of subsets $CX3CR^+CD8^+$ and HLA-DR^+CD8^+ between T_{null} and T_{MART-1} (Fig. 4). It might be the reason why TCR-T_{MART-1} were more cytotoxic than T_{null} (Fig. 2).

IV. Conclusions

In conclusion, the landscape of different functional cell clusters in T_{null} and TCR-T_{MART-1} responding to different proportions of PD-$L1^+$ MEL-526 cells loaded with MART-1_{27-35} peptide was provided in this study.

V. Materials and Methods

a) Cell culture

HEK293T (ATCC, CRL-11268) cell line was purchased from ATCC, and MEL-526 (BNCC340404) cell line was purchased from BNCC, and they were cultured in DMEM (Gibco, 21063029) added with 10% fetal bovine serum (Hyclone, SH30084.03HI), penicillin (100 IU/mL), and streptomycin (50 μg/mL) at 37℃ and 5% CO2. $CD8^+$ T cells were cultured in HIPP-T009 (Bioengine, RG0101302) containing 2% fetal bovine serum (Hyclone, SH30084.03HI), IL-2 (20 ng/ml), IL-7 (10 ng/ml) and IL-15 (10 ng/ml) at 37℃ and 5% CO_2.

b) Peptide

HLA-A*0201-restricted MART-1 peptide ELAGIGILTV) was synthesized by GenScript (Nanjing, China). The peptide was stored at 10 mg/ml in 100% dimethyl sulfoxide (DMSO; Sigma-Aldrich) at -20°C.

c) Plasmid construction

The constant regions of TCR_{MART-1} sequence, which was identified from our previous work (data

unpublished), were replaced by mouse TCR constant region α and β, respectively. TCR_{MART-1}-encoded DNA was then synthesized by GeneScript (Nanjing, China) and ligated into a lentiviral vector, pRRLSIN.cPPT.PGK (Addgene, 12252).

d) Lentivirus production

To produce lentivirus, 293T cells were transfected with a lentiviral vector containing the gene of interest and the packaging constructs (PsPAX2 and PMD2G). The culture medium was collected 72 h after transfection and filtered with 0.45 uM filters (Sartorius). Subsequently, the virus was concentrated by ultracentrifugation at 35,000 rpm for 90 min.

e) Generation of MART-1 peptide-specific TCR-T cells

Human Peripheral Blood Mononuclear Cells (PBMCs) were isolated from the blood of HLA-A*0201-restricted healthy donors with informed consent. $CD8^+$ T cells were purified from PBMC via human CD8 MicroBeads (MiltenyiBiotec) and activated with T Cell TransAct (MiltenyiBiotec); 36-48 h after activation, $CD8^+$ T cells were transduced with lentivirus in a 6-well or 12-well plate. To promote infection efficiency, polybrene was added into the medium at the final concentration of 2μg/mL, and the well plate was centrifuged at 800g for 30 minutes. T cells were then expanded and maintained in T cell medium.

f) In vitro killing assays

TCR-T cells were co-cultured with target cells labeled with Carboxyfluoresceinsuccinimidyl ester (CFSE; Invitrogen) at different E: T ratios for 24 h. Cells were then collected and stained with PI for FACS analysis. The cytotoxicity was calculated with the proportion of PI^+ $CFSE^+$ cells divided by the proportion of $CFSE^+$ cells.

g) Statistical analysis

PRISM 6 (GraphPad Software) and RStudio were used for data analysis. *P<0.05, **P<0.005, ***P<0.001. Error bars represented the Mean±SD.

h) Differential gene expression analysis

Seurat FindMarkers were used for DEG analysis. DEGs of each subset were generated relative to all the remained cells. Then DEGs were identified as the criteria: FDR adjusted p value of F test < 0.01.

i) Gene set enrichment analysis

The "enrichGO" function in the "clusterProfiler" package was used to perform GO analysis with the corresponding default parameters. Pathways with the q value <0.05 corrected by FDR were used for further analysis.

j) Data availability

The data that support the findings of this study have been deposited into CNGB Sequence Archive (CNSA: https://db.cngb.org/cnsa/) of CNGBdb with accession numberCNP0001109.

k) Ethics approval and consent to participate

The study was approved by the Institutional Review Board on Bioethics and Biosafety of BGI. Written informed consent forms were regularly obtained from all donors.

Acknowledgements

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Author contributions

Q.G. designed and supervised the project, wrote and revised the manuscript. S.L. performed the bioinformatic analysis. R.D., H.C. and Q.G. performed the experiments. B.K., Y.G. and X.D. helped with the manuscript revision.

Declaration of interests

The authors declare no competing financial interest.

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Figure legend

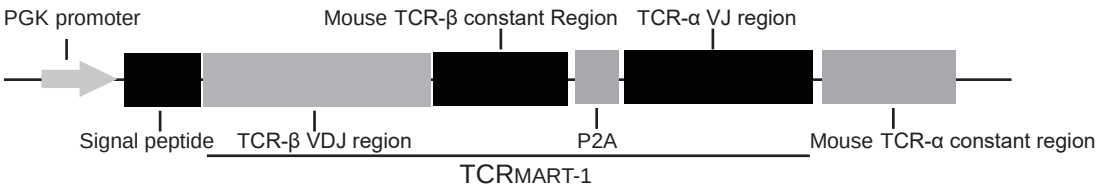

Figure 1: Schematic design of MART-1$_{26-35}$ peptide-specific TCR sequence. The transcription of TCR_{MART-1} was driven by PGK promoter. Mouse constant regions were used to reduce the mispairing with endogenous TCR. TCRβ and TCRα were linked by P2A.

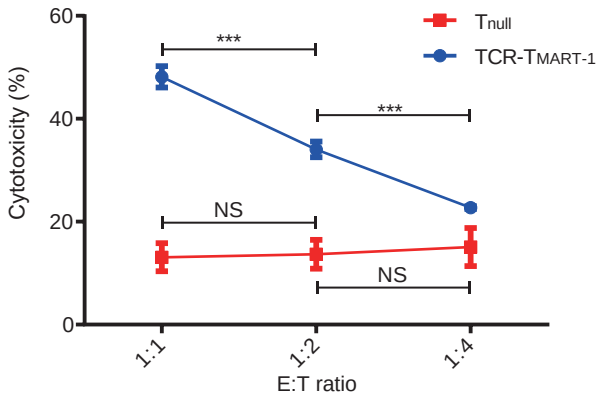

Figure 2: Cytotoxicity of T_{null} and TCR-T_{MART-1} against peptide-loaded MEL-526 cells. The in vitro killing assays were performed at different E: T ratios (1:1, 1:2, and 1:4). Data were generated from three individual replicates and shown as mean ± SD. 2-tailed unpaired t-tests were used to calculate p-values, *: p＜0.05; **: p＜0.01; ***: p＜0.001; NS: Not significant.

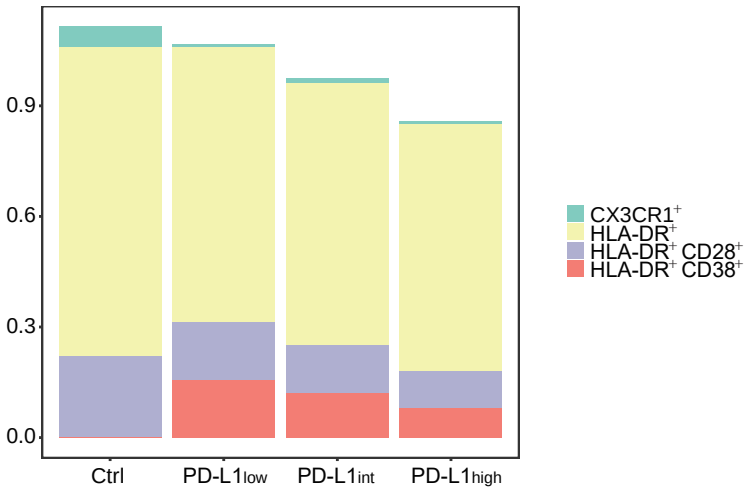

Figure 3: Compositions of specific cell clusters in T cells responding to tumor PD-L1. The proportions of clusters $CX3CR1^+$, $HLA\text{-}DR^+$, $HLA\text{-}DR^+CD28^+$, and $HLA\text{-}DR^+CD38^+$ in T cells stimulated with antigen or not.

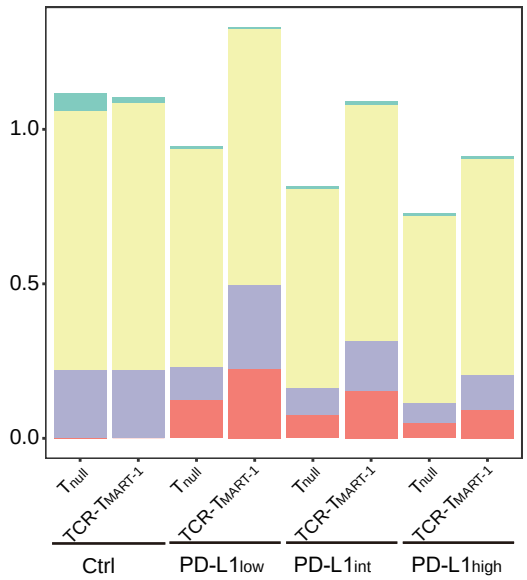

Figure 4: Compositions of specific cell clusters in T_{null} and TCR-T_{MART-1} responding to tumor PD-L1. The proportions of clusters CX3CR1^{+}, HLA-DR^{+}, HLA-DR^{+}CD28^{+}, and HLA-DR^{+}CD38^{+} in T_{null} and TCR-T_{MART-1} stimulated with antigen or not.

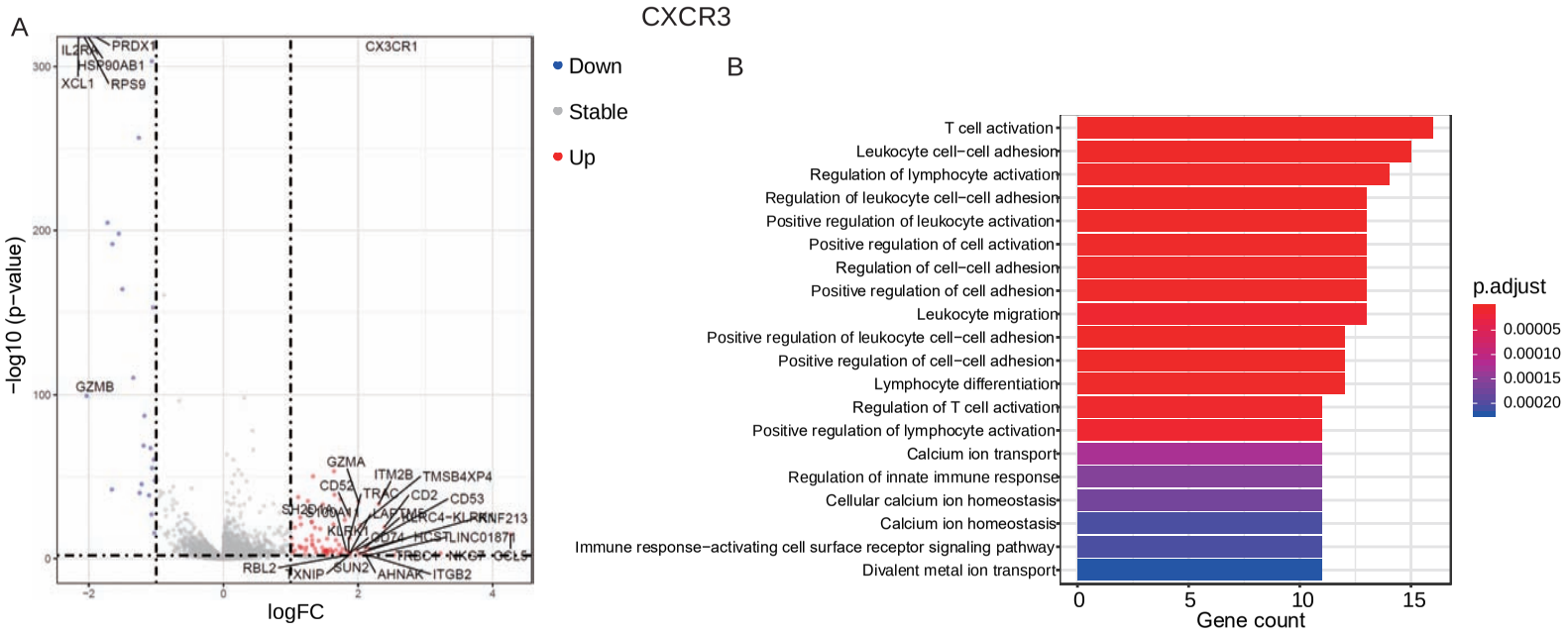

Figure 5: Characteristics of cluster CX3CR1⁺CD8⁺. A, Volcano plot showing differentially expressed genes between CX3CR1+ and CX3CR1- T cells. Each red or blue dot denotes an individual upregulated or downregulated gene (|logFC| >= 1 and p.value< 0.01). B, Bar plot showing the top 20 pathways of CX3CR1⁺CD8⁺ T cells. The color represents p.value and the x-axis represents gene count.

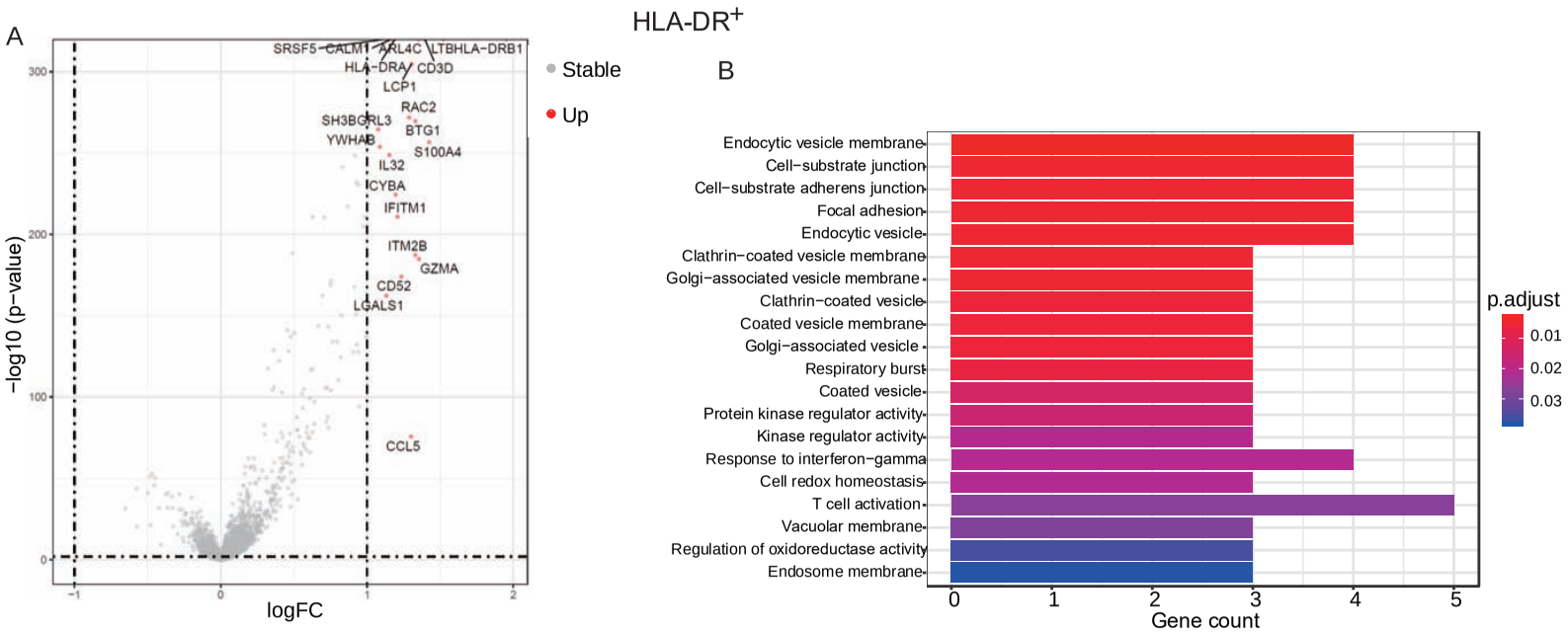

Figure 6: Characteristics of cluster HLA-DR$^+$CD8$^+$. A, Volcano plot showing differentially expressed genes between HLA-DR$^+$ and HLA-DR- T cells. Each red or blue dot denotes an individual upregulated or downregulated gene (|logFC| >= 1 and p.value< 0.01). B, Bar plot showing the top 20 pathways of HLA-DR$^+$CD8$^+$ T cells. The color represents p.value and the x-axis represents gene count.

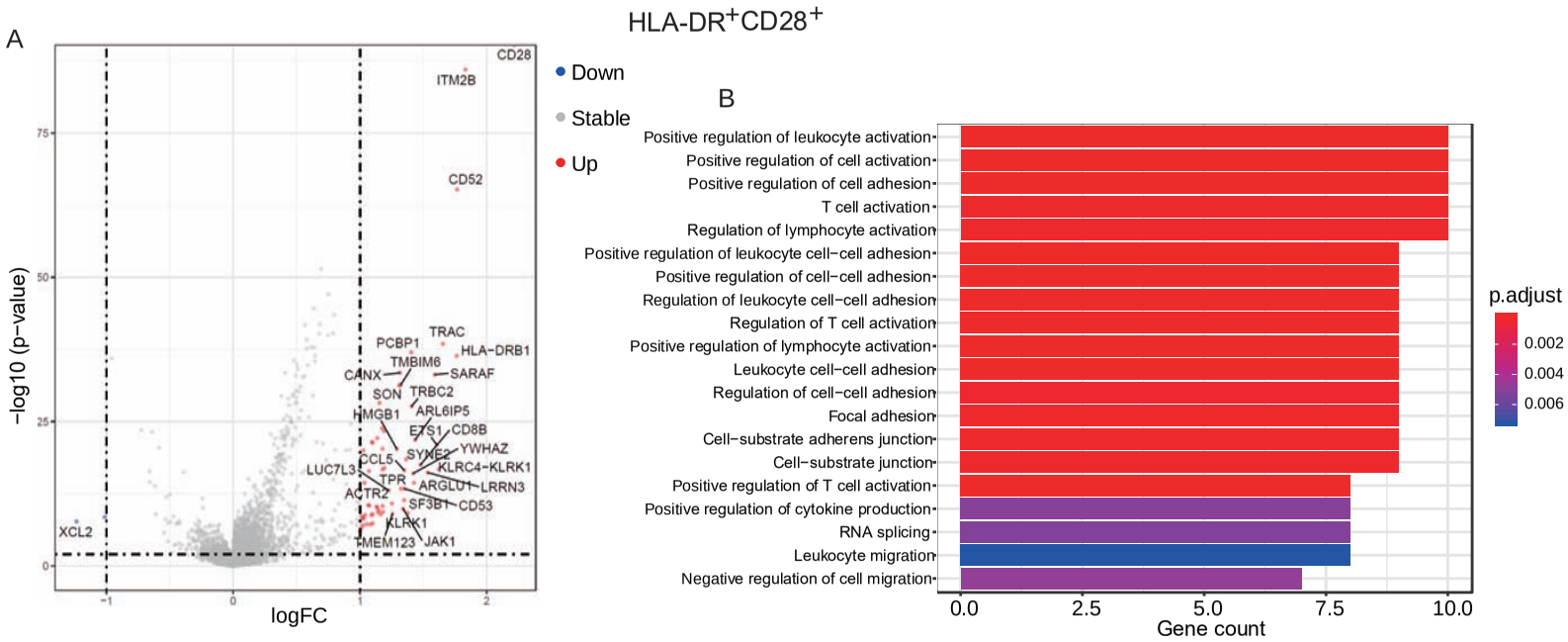

Figure 7: Characteristics of cluster HLA-DR$^+$CD28$^+$CD8$^+$. A, Volcano plot showing differentially expressed genes between HLA-DR$^+$CD28$^+$ and non-HLA-DR$^+$CD28$^+$ T cells. Each red or blue dot denotes an individual upregulated or downregulated gene (|logFC| >= 1 and p.value< 0.01). B, Bar plot showing the top 20 pathways of HLA-DR$^+$CD28$^+$CD8$^+$ T cells. The color represents p.value and the x-axis represents gene count.

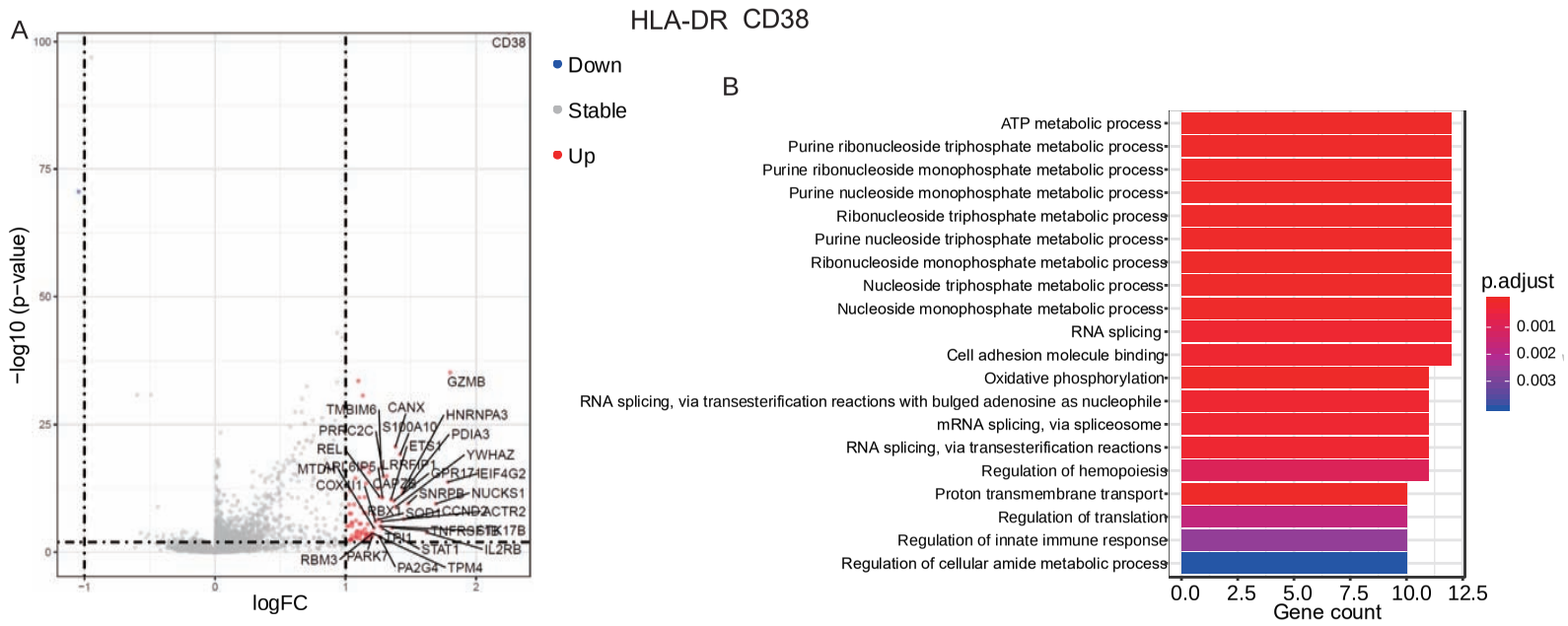

Figure 8: Characteristics of cluster HLA-DR$^+$CD38$^+$CD8$^+$. A, Volcano plot showing differentially expressed genes between HLA-DR$^+$CD38$^+$ and non-HLA-DR$^+$CD38$^+$ T cells. Each red or blue dot denotes an individual upregulated or downregulated gene (|logFC| >= 1 and p.value< 0.01). B, Bar plot showing the top 20 pathways of HLA-DR$^+$CD38$^+$CD8$^+$ T cells. The color represents p.value and the x-axis represents gene count.

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Matily Herbal Drink May Reduce Oxidative Stress, Hyperglycemia, and Hyperlipidemia and Increases Immunity-Case Study Reports

By John T. Eapen

Introduction- Oxygen is an element indispensable for all aerobic organisms to sustain life (1). Cells produce energy mainly in the mitochondria through oxidative phosphorylation, a series of electron transfer in the Electron Transport Chain (ETC), where oxygen is the final electron acceptor. During this process, it creates free radicles by the mitochondria. Oxidative stress produces free radicals. A 70 Kgs man may produce nearly 2 Kg of free radicals in his body in a year (2). It is comparatively a huge amount. Examples offree radicals with one or more unpaired electrons are superoxide, hydroxyl, andnitric oxide radicals (1, 3).

A molecule like oxygen is stable when it shares its electrons in the paired state, when it loses or gains an extra electron, it becomes unstable. This condition leads them to "steal" or take it from other biomolecules. This process leaves the biomolecules in the oxidative state, which can start pathological conditions. For example, when Low-Density Lipoproteins when becomingoxidized, causes atherosclerosis in the blood vessels and cause plaques inside the arteries (4).

GJMR-F Classification: NLMC Code: QW 540

MATILYHERBALDRINKMAYREDUCEOXIDATIVESTRESSHYPERGLYCEMIAANDHYPERLIPIDEMIAANDINCREASESIMMUNITYCASESTUDYREPORTS

Strictly as per the compliance and regulations of:

Matily Herbal Drink May Reduce Oxidative Stress, Hyperglycemia, and Hyperlipidemia and Increases Immunity- Case Study Reports

John T. Eapen

I. Introduction

Oxygen is an element indispensable for all aerobic organisms to sustain life (1). Cells produce energy mainly in the mitochondria through oxidative phosphorylation, a series of electron transfer in the Electron Transport Chain (ETC), where oxygen is the final electron acceptor. During this process, it creates free radicles by the mitochondria. Oxidative stress produces free radicals. A 70 Kgs man may produce nearly 2 Kg of free radicals in his body in a year (2). It is comparatively a huge amount. Examples offree radicals with one or more unpaired electrons are superoxide, hydroxyl, andnitric oxide radicals (1, 3).

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Oxidative stress and disease remained a chicken and egg puzzle for a long time. Earlier it was believed that disease caused oxidative stress in the human body. Now the consensus among medical fraternity is that oxidative stress leads to various disease conditions.

"The human body has several mechanisms to counteract oxidative stress by producing antioxidants, which are either naturally produced in situ, or externally supplied through foods and/or supplements"(1). Antioxidants provide electrons needed for the stressed molecules and eliminate the free radicals (5).

There are many biochemical markers to measure the quantity of free radical status in the body. An excessive free radical produces fatigue in the human body, and we could take this as a general standard for the common man to assess the status of his body. Thus wellness of human health is inversely proportional to the free radicals in the body.

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In this communication, we want to report a herbal drink (Matily Drink) we designed with natural products and tested in patients as case studies and among some volunteers. The pharmacological means of controlling hyperglycemia and hyperlipidemia are expensive for the poor masses without and income and insurance. Hence we developed a drink with natural ingredients and tested as a case study and on some volunteers. It reduced weight, hypoglycemia, and hyperlipidemia and gave better wellness feeling, even relieving wheezing difficulty in the patient.

In another case study, with a person who was a chain smoker and had a frequent cough, found relief for his cough after taking the drink for a month.

All the volunteers reported wellness feeling and found that they were energetic after taking this drink.

Based on these encouraging results, we were about to commercialize the product. However, now in the corona pandemic season, we bring it to the public domain hoping this drink may help people to boost their immunity and also some clinicians will try it on COVID 19 patients to see whether the severity of lung infection is reduced, as we found some benefit to the lungs in the above case studies.

II. Rational behind Designing and Testing of Drink

In December 2017, an elderly male patient of 62 years with a history of cardiac asthma presented his case to a cardiologist. The cardiologist wanted to rule out ischemic cardiac asthma and suggested to the patient to undergo an angiogram. He prescribed the following medicines for the patient. Glucophage for blood sugar, Starvas to lower cholesterol, Clopilet A for thinning of blood, Losar 50 for blood pressure, Selaken XL as beta-blocker, Imdur 30mg for angina, and Dytor 10mg to remove excess water from the body.

The patient was already on Loser 50 for his blood pressure and he continued the same from the prescription list. He did not take other medicines because he was not sure whether he could take the medications regularly because of his poor economic condition. He took Dytor whenever he felt bloated. Proper exercises reduced bloated feeling, and in those days, he avoided Dytor.

The patient had diabetics for seven years. In the beginning, he took medication for one month, and he was feeling starving after taking the medicines. So he discontinued medication and started with diet and exercise to control the blood sugar levels. He used to take a small quantity meal four or five times a day. He used to walk at least two kilometers every day.

With the above prescription in his hand, the patient was searching for natural products that will help his condition. He developed a herbal drink with the following ingredients, and the reasons for selecting them are in the reference.

Okra has antidiabetic and anti-fatigue properties. It also reduces hyperlipidemia (6,7). Mint leaves stimulate bile secretion, which uses cholesterol in the blood and may thus reduce cholesterol levels in the blood naturally (8). Curry leaves are good for liver as it has got anti hepatotoxicity effect (9,10). Ginger has medicinal properties, and it has blood-thinning capability (11,12). Lemon has various properties, and it is rich in Vitamin C (13,14). Sometimes, we used lemon with its peels for making the drink. We mention elsewhere the health benefits of lemon peels (15). Sea salt with no anti-caking agent and sugar was added for taste (optional).

All ingredients and about 200 ml water was added in a blender. It was ground and blended with water for a few minutes. It was made up to 750 ml, and filtered through a strainer. When the constituents were whipped well, there was no trace of mucilage of okra in the drink.

We give a concoction and procedure in note 1.

III. Results and Discussion

Table 1 shows different parameters before and after taking the drink.

Table 1: The weight, blood glucose, total cholesterol, HDL and LDL in the patient before and after taking Matily Drink

Parameters measured	Before taking the drink	After taking the drink	
	12/12/2017	24/03/2018	19/06/2018
Blood glucose (mg/dl) (random)	271	–	
Blood glucose fasting (mg/dl)	–	123.5	134.7
Blood glucose postprandial (mg/dl)	–	167.5	156.9
Total cholesterol (mg/dl)	220	182.7	–
HDL (mg/dl)	38.0	44.0	–
LDL (mg/dl)	130	128.0	–
Body weight (Kgs)	95	89	86

Table 2: Lipid profile after taking Matily Drink for three months

Test	Value	Units	Ref Range
Appearance	Clear		
S. Total cholesterol	182.7	Mg/dl	140 - 240
S.HDL Cholesterol	44.0	Mg/dl	30 - 65
Triglycerides	94.4	Mg/dl	25 - 160
LDL cholesterol	128.0	Mg/dl	0 - 130
S.VLDL Cholesterol	28.0	Mg/dl	10 - 30
TC/HDLC ratio	4.1	Mg/dl	3 - 5
LDLC / HDLC ratio	2.9	Mg/dl	Up to 3.5

Results are shown in Tables 1 and 2 shows that Matily drink had some beneficial benefits to the patient.

The weight of the patient reduced from 95 kgs to 86kgs in about six months with no crash dieting or

excess exercises. It was a natural way of shedding weight. It remained in that state as long as the patient limited his calorie intake was same and continued his daily walk of two km.

The total cholesterol of the patient was always between 220 to 240 mg/ dl in the past. But within three months, it lowered the total cholesterol to 182 mg/ dl. Similarly, HDL cholesterol was always between 35 to 38 in the past. It rose to 44 mg/dl within three months' with Matily Drink. Total cholesterol / HDL Cholesterol ratio was 4.1, and the LDL cholesterol / HDL cholesterol was 2.9, which was within the acceptable range (Table 2).

Matily, Drink influenced the blood sugar of the patient. The patient always took a limited amount of free sugar in his tea. He never avoided free sugar. His random blood sugar was 271 mg/dl in the beginning before he started taking Matily Drink. In three months, the fasting sugar was 123.5 mg /dl, and postprandial sugar was 167.5 mg /dl.

The patient had some wheezing problems in the beginning before starting the course. However, it reduced with Matily Drink. Before taking the MatilyDrink patient had difficulty climbing steps, especially in the morning when the temperatures were down. However, maybe because of weight reduction, reduction of blockage of blood vessels and, or improved microbiome in the gut, patient stopped having difficulty in climbing steps.

The case study presented here shows that certain natural products can control hyperglycemia and hyperlipidemia without depending on pharmacological methods. Cholesterol is essential for the body, and our body produces it in the liver. The patient did not prefer the use of statins to manipulate the synthesis of cholesterol by the liver. Similarly, instead of depending on pharmacological methods to change the blood thinning process, he preferred natural products like ginger. The drink also improved his lung function, and it reduced wheezing problems.

In another case study, a 48-year-old male on chain-smoking of, "beedies", a crudely prepared cigar, took Matily drink to boost his immune system during COVID 19 lockdown. He always had frequent cough, and it disappeared after one month.

We mention the properties of the ingredients used in the drink and its benefits on human health in the references given.

To conclude: In the case-studies given above show the benefits of Matily drink, especially to those who cannot afford pharmacological methods. The wellness feelings reported by volunteers could show the reduction of free radicals in their bodies with the drink. It reduces free radical generation in the human body when hyperglycemia and hyperlipidemia are under control. The body will increase its immunity. Since Matily drink shows a beneficial effect on the functioning of lungs, it is worth checking whether it could reduce the severity of disease in the COVID 19 patients.

Note 1. Preparation of Matily Drink
Okra - one small one
Ginger - about 2 cm long
Mint - 2 or 3 leaves
Curry leaves - 2 or 3 leaves
Lemon - one
Sea salt - to taste
Sugar - to taste

All these were blended in a mixer with about 200ml water, and finally strained. The total volume was made to 750 ml with water and the drink was consumed throughout the day.

Disclaimer: Any patients on pharmacological methods to control blood sugar, cholesterol, and blood thinning process should try this drink only under medical supervision.

Acknowledgments

The author named the drink as Matily in remembrance of his father, Mr. M.E. Eapen (1926–2018), known among his American friends as "MAT" and who continuously encouraged the author to innovate methods to ease the suffering of the afflicted.

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Pericardial Effusion Caused by Renal Carcinoma of Clear Metastatic Cells: A Rare Cause of Cardiac Tamponade

By Erlon de Avila Carvalho, MD, Marina Varela Braga de Oliveira, MD, Rafael Reis, MD, Isabela Oliveira Campos, MD, Rafael Brito Fontella, MD, Ricardo José Pinheiro Reis Filho, MD & Júlio Rezende de Andrade, MD

Resume- Objective: To report the case of a patient with renal cell carcinoma of the clear cell type with the presence of metastatic disease at diagnosis, affecting the adrenal, lung and pericardium. Evolving with cardiac tamponade and need for urgent surgical intervention, being performed through thoracoscopy, a pericardiectomy for making a pericardial window.

Method: The information was obtained by reviewing the medical record, interviewing the patient, photographic record of the diagnostic methods to which the patient was submitted and literature review.

Final considerations: The reported case brings to light the description of a common clinical condition in medical centers in this case, cardiac tamponade, caused by renal carcinoma of which cardiac metastatic presentation represents a low index, and the need for urgent surgical intervention as an outcome.

Keywords: cardiac tamponade, rcc renal cell carcinoma, clear cell carcinoma, metastasis, pericardiectomy.

GJMR-F Classification: NLMC Code: WP 460

Pericardial Effusion Caused by Renal Carcinoma of Clear Metastatic Cells: A Rare Cause of Cardiac Tamponade

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Keywords: cardiac tamponade, rcc renal cell carcinoma, clear cell carcinoma, metastasis, pericardiectomy.

I. Introduction

Kidney cancer makes up 2% to 3% of adult malignancies, with an incidence of 7 to 10 cases per 100,000 inhabitants in the most developed regions of Brazil [123]. In these cases, clear cell carcinoma represents 81%, followed by papillary carcinoma, which is responsible for about 14% of kidney cancer cases [4]. It is estimated that about 16% of patients are diagnosed with metastatic disease [5]. Cardiac and pericardial metastasis is rare [4]. In the period from 1935 to 1998, there were only 131 cases of cardiac tamponade as an initial manifestation of underlying malignancy [6]. In this case, the patient described in this report developed cardiac tamponade, an event that is triggered by a pericardial effusion. It is a condition that needs urgent intervention. Among the causes, metastatic spread of malignant diseases is an uncommon cause, being clinically silent in most cases [7]. In rarer situations, the clinical presentation can be present, be variable and delay the patient's diagnosis, which is essential to be performed early to reduce morbidity and mortality [8]. We report a case of cardiac tamponade caused by metastasis of a clear cell renal tumor and discussed the symptoms, diagnostic methods and the need for urgent surgical intervention through thoracoscopy, pericardiectomy and making a pericardial window.

II. Case Report

Male patient, 49 years old, admitted to Hospital Alberto Cavalcanti in Belo Horizonte - MG, Brazil, on 04/23/2020 with dyspnea and cough started 6 months ago, associated with weight loss of 5kg. He sought care due to persistence and worsening of symptoms, presenting on admission: orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion and cough that was accentuated in the supine position. Without fever, sputum or flu-like symptoms, a previous diagnosis of COPD of undetermined origin had already been made, and heart failure was questioned. During the physical examination, he noticed the presence of a mass in the left hypochondrium and lymph node enlargement in the left cervical chain. Computed tomography of the chest and abdomen showing a mass in the left kidney of 15 cm, suggestive of primary neoplasia. Mediastinal lymph node enlargement, bilateral micro pulmonary nodules and 2.7 cm adrenal mass, suggestive of secondary neoplasia (figure 1)

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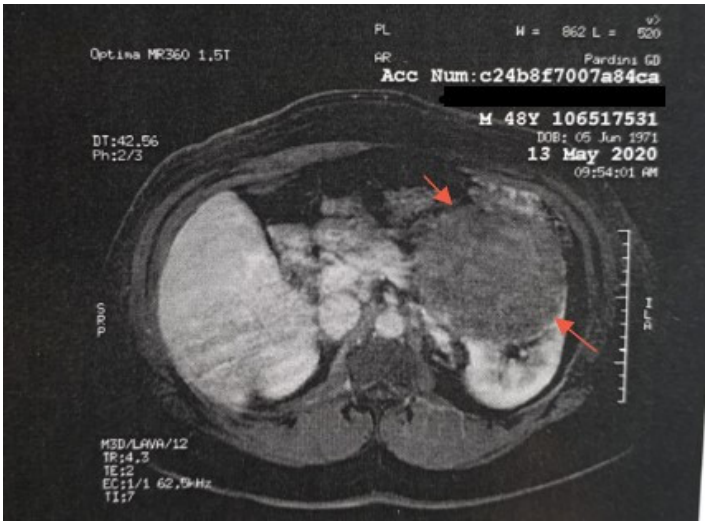

Figure 1: RED ARROW: Delimitation of the left renal tumor

It was evaluated by Oncology with the anatomopathological of the cervical lymph node showing fragments of lymph nodes with atypical epithelial cells, some with clear cytoplasm, forming solid masses and papillary structures infiltrating parenchyma. Immunohistochemistry showed metastatic clear cell carcinoma, a positive study for cytokeratin and diffuse expression for PAX8. The findings favor that the kidney is the site of origin for this metastatic carcinoma.

To rule out heart failure, a transthoracic echocardiogram with preserved systolic and diastolic function and normal BNPs was performed. Since 05/17, the patient has presented progressive worsening of the respiratory pattern and refractoriness to clinical treatment. On 05/24, the patient was evaluated in bed, with respiratory worsening, tachycardia, jugular engorgement, paradoxical pulse, pain in the right hypochondrium, orthopnea, auscultation with expiratory wheezing and light crackling. Urgent ultrasound was performed, identifying pericardial effusion and indirect signs of cardiac tamponade (Figure 2). Thoracic surgery was requested to be evaluated due to the patient's instability, and he was immediately referred for a surgical approach, where thoracoscopy was performed. 10 cm incision in the region of the 6th left intercostal space with 10mm trocars and 30mm optic passages within the left hemithorax inventory. Engorged pericardial effusion was identified with subsequent opening of the pericardium with a Hook cautery pen and elimination of bloody liquid (Figure 3). Pericardial window and pericardiectomy of about 2 cm^2 were performed (Figure 4). Approximately 200ml of hematic pericardial content was aspirated, and there was an instant improvement in hemodynamic parameters. Pericardial material and pericardial implant were collected for biopsy. Finally, water seal pleural drainage was performed. Anatomopathological examination of the pericardial biopsy confirmed metastatic implantation. There were no complications in the postoperative period, a chest tube was removed on the 12th postoperative day, and the patient was discharged on 06/16/2020, referred to the clinical oncology clinic for therapeutic follow-up.

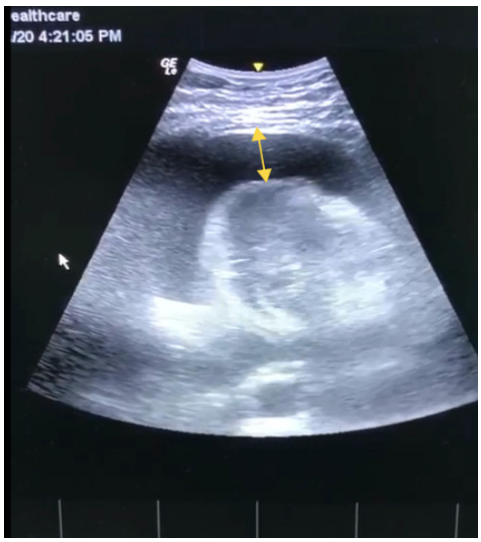

Figure 2: Yellow Arrow: Pericardial Effusion

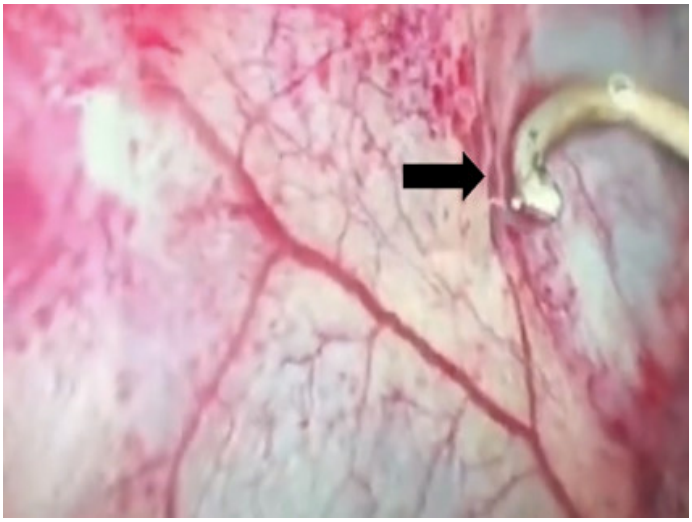

Figure 3: Black Arrow: HOOK forceps in contact with pericardial membrane

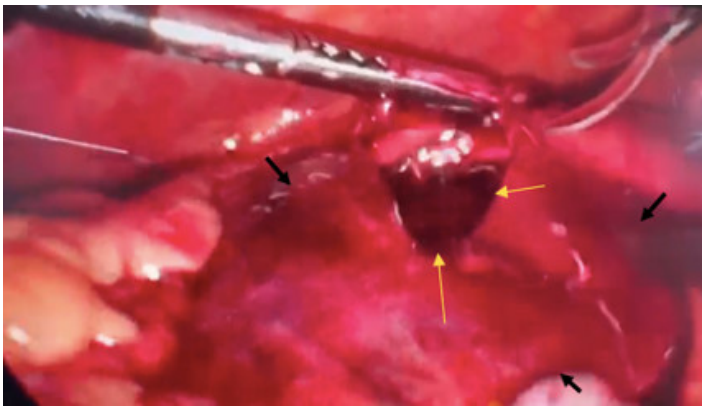

Figure 4: BLACK ARROW: Pericardial sac YELLOW ARROW: Pericardial window

III. Discussion

Malignant tumors represent 32% of the causes of cardiac tamponade [9]. Pericardial metastases have been reported in 15.4% of cases of malignant autopsied tumors, but most are asymptomatic and rarely cause clinical repercussions [10]. According to Oliver et al. [11], the main primary malignant tumors with pericardial metastasis are lung cancer 36.5%, breast cancer 22.3%, leukemia and malignant lymphoma 17.2% and renal cancer 1.9%. As a metastatic route for pericardial metastases, it is speculated that it is done by retrograde lymphatic transit [12].

In the period from 1935 to 1998, there were only 131 cases of cardiac tamponade as an initial manifestation of underlying malignancy. The main primary cancers causing effusion were: lung (52 cases), lymphomas and leukemias (17 and 19 cases respectively). Only one case of renal cell cancer was reported during this period [6]. A study carried out between January 1, 1999 and January 31, 2003 evaluated 219 patients with pericardial effusion, 96 patients had the disease related to malignancy, only one positive case for renal cell cytology (table 1). [13]

Table 1: Underlying Malignancy among 96 Patients with Cancer-Related Pericardial Effusion

	Patients	
Site	No.	%
Lung	33	34.4
Breast	16	16.7
Leukemia/myelodysplastic syndrome	9	9.4
Cancer of unknown primary	8	8.3
Esophagus	5	5.2
Sarcoma	5	5.2
Mesothelioma	4	4.2
Lymphoma/lymphoproliferative disorder	4	4.2
Colorectal	4	4.2
Other*	8	8.3
Total	96	100.0

**Other malignancies: cervical (2), head/neck, eccrine gland, nerve sheath, ovarian, prostate, renal cell. [8]*

The frequency of cardiac tamponade as the initial manifestation of malignant effusion is highly variable and depends on the rate of fluid accumulation, fluid volume and underlying cardiac function. The pericardium can be stretched for a period to accommodate a large volume of fluid before the clinical appearance of the tamponade. The signs and symptoms of cardiac tamponade include dyspnea, orthopnea, low output (peripheral vasoconstriction, cold and wet extremities, poor capillary filling and diaphoresis), jugular venous distention, muffled heart sounds, paradoxical pulse and reduced pulse pressure. Even with cancerous pericarditis, in the case of kidney cancer, performing pericardiocentesis not only reduces symptoms, improving heart failure, but also prolongs the period of survival. The median overall survival of patients with malignant pericardial effusion is less than 6 months [14].

In the present case report, we narrate a case of clear cell renal cell carcinoma, the first symptoms presented by the patient were cough and dyspnea, although the first echocardiogram did not show significant changes and the patient had a previous COPD to clarify, the treatment established for COPD and HF were not effective. The symptoms presumably were due to the ongoing pericardial effusion. One week after CT showing bilateral pleural effusion and small pericardial effusion, with the exacerbation of cardiac symptoms, ultrasound at the bedside was performed, which showed an important pericardial effusion with cardiac tamponade.

Videoracoscopy and pericardiectomy were indicated by the surgical team. Videothoracoscopy was chosen because it is less invasive than open thoracotomy, the pericardial approach through electro-cauterization could be performed by a previous study via POCUS, better viewed in the lower left parasternal window. Approximately 550 ml of hematic pericardial content was aspirated, with instant improvement in hemodynamic parameters.

Although simple pericardiocentesis can save lives in cases of cardiac tamponade, this procedure alone is rarely an adequate therapy due to the high rate of fluid buildup. To avoid recurrence, the patient received immunotherapeutic treatment and pericardiectomy was performed against urgent pericardiocentesis, provided by the shunt in the pericardial window in the case confirmed by the pathology of clear renal cell metastasis. Clear cell renal cell carcinoma that presents as cardiac tamponade is rare in the literature. The case also emphasizes the importance of a complete review of the history, physical examination and complementary examination, in addition to exposing the need to perform a resolutive surgical procedure.

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Epidemiological Aspects of Dysphonia in Tertiary Care Hospital

By Dr. A H M Delwar, Dr. Kishor Kumar Halder, Dr. Nurul Karim Chowdhury & Dr. A B M Tofazal Hossain

Abstract- *Objective:* To find out the prevalence, etiology, risk factor, presentation and treatment option of the dysphonic people, facilitate the prevention of the risk and predisposing factor of it.

Study Design: Cohort retrospective study.

Setting: Academic tertiary care medical centre.

Subjects and Methods: A total of 1739 dysphonic patient's demographic data collection and analyzed, in the department of Otolaryngology and Head-Neck Surgery, Comilla Medical College, and Comilla Medical Centre, Bangladesh from 01 July 2016 to 31 June 2019.

Results: The incidence of dysphonic patients was1.16%, and the yearly prevalence of 33.33%. Out of 1739, the male was 1006 (57.85%), and the female was 733 (42.15%), 50-59 years were highest presentation 488 (28.06%). Among 1739, non-specific chronic laryngitis was 1015 (58.37%), dysphonia without structural change (MTD) 417 (23.98%), and malignancy 90 (5.17%). Off them, smoker was 911 (52.39%), voice abuser 469 (26.97%), industrial worker was 477 (27.43%), teacher 359 (20.64%), singer 151 (8.68%), and slum dweller was 528 (30.36%).

Keywords: *dysphonia, chronic laryngitis, muscle tension dysphonia (MTD), rigid telescopic video laryngoscopy (RTL).*

GJMR-F Classification: *NLMC Code: QZ 220*

Strictly as per the compliance and regulations of:

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Setting: Academic tertiary care medical centre.

Subjects and Methods: A total of 1739 dysphonic patient's demographic data collection and analyzed, in the department of Otolaryngology and Head-Neck Surgery, Comilla Medical College, and Comilla Medical Centre, Bangladesh from 01 July 2016 to 31 June 2019.

Results: The incidence of dysphonic patients was1.16%, and the yearly prevalence of 33.33%. Out of 1739, the male was 1006 (57.85%), and the female was 733 (42.15%), 50-59 years were highest presentation 488 (28.06%). Among 1739, non-specific chronic laryngitis was 1015 (58.37%), dysphonia without structural change (MTD) 417 (23.98%), and malignancy 90 (5.17%). Off them, smoker was 911 (52.39%), voice abuser 469 (26.97%), industrial worker was 477 (27.43%), teacher 359 (20.64%), singer 151 (8.68%), and slum dweller was 528 (30.36%). Presenting features revealed hoarse voice, reduced loudness, and tiring to talk above 90%. All patients assessed by the rigid Hopkin's telescope. Non-neoplastic benign, and suspected malignant lesion was 1503 (86.43%), neoplastic benign and malignancy was 236 (13.57%), conservatively treated 1512 (86.94%), and surgically 227 (13.6%) treated by micro-laryngeal surgery.

Conclusion: Dysphonia affect more than 33% of people at some point of life. It definitely influences the quality of life and losing patient health and wealth. Early and effective treatment decreases the further loss.

Keywords: dysphonia, chronic laryngitis, muscle tension dysphonia (MTD), rigid telescopic video laryngoscopy (RTL).

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I. Introduction

Normal voice is a key factor to maintain the standard quality of life. Dysphonia makes the patient isolated, which may induce his stress, anxiety, and depression [1]. There are four causes of dysphonia: 1. Inflammatory. 2. Structural or Neoplastic. 3. Neuromuscular. 4. Muscle tension dysphonia [2]. The assessment of singers, teachers, and other professional voice users, an understanding of their Occupational and voice requirements is essential [3] [4] [5]. Chronic laryngitis occurs due to upper and lowers respiratory tract infection gave the decision by Steel and McLoughlin in 1976 in their research paper [6]. Chronic laryngitis is directly related to occupations like excess noise at work [7], asbestos workers [8], cement workers [9], solvents and shoe workers [10]. The allergy is related to chronic laryngitis, which directly affects larynx and lung [11]. Gastro-esophageal (GERD) and laryngopharyngeal reflux (LPR) is one of the debating etiological factors of chronic laryngitis [12]. Candidal infection causes chronic laryngitis, usually seen in patients of post-irradiated, immune-compromise state, diabetes mellitus, after prolonged antibiotic administration [13]. Smoking is the key factor of chronic laryngitis [14]. MTD has multiple primary causes, includes 1. Stress, anxiety and depression. 2. Conversion disorder. 3. Poor vocal hygiene [15]. Laryngeal carcinoma is one of the commonest sites of malignancy which mainly affect men cause dysphonia [16]. A true vocal cord polyp arises from the free edge of vocal cord which size is greater than 03 mm [17]. Vocal cord nodules are small bilateral swelling less than 03 mm size, produce dysphonia and occur in student, teacher, singer, and leader [18]. Vocal cord paralysis is another prime cause of dysphonia, which may be iatrogenic and idiopathic, may be unilateral or bilateral [19]. Reinke's edema is chronically and irreversibly, polypoidal swelling of vocal cords, also known as smoker's larynx [20]. Leukoplakia, TB laryngitis, papilloma, ulcer, and cyst are minor causes of dysphonia.

II. Methods and Materials

The study performed in two tertiary care hospitals. During the three years period, 116128 patients attended in the outpatient department of the Government Comilla Medical College Hospital, and

33840 in the Private Comilla Medical Centre, concern Clinic of Central Medical College, Comilla. Out of 149968, the laryngeal disarrayed patient was 1739. Firstly, the dysphonic patient consulted with the village doctor (Health Assistant) in the shop of the drug, and Community Health Worker (Government) working in the primary care preventive non-bedded hospital. Secondly, they consulted with the Graduate Doctor who works in the secondary care hospital named 50 bedded Upazilla Health Complex. The patient came to the tertiary care hospital after suffering from dysphonia from one month to one year. We performed the endoscopic assessment of all patients with rigid Hopkin's telescope (RTL). Some patient examined by traditional l/L and FOL. The patient and attended if the patient is children gave written informed consent about the examination procedure. The following information collected about the patient: Gender, age, personal history, occupation, residence, predisposing factor, presenting feature, investigation, disease pattern, and treatment option. Descriptive statistics used to calculate the data. Figures and tables citeted by Microsoft word 2007.

III. Results

The incidence among outpatient was 1.16%, and the yearly prevalence of 33.33%. Among them, the male was 1006 (57.85%), and the female was 733 (42.15%) Figure-1, patient wasn't found between 0-9 years, 10-19 years were 191 (10.98%), 20-29 years 208 (11.96%), 30-39 years 226 (13%), 40-49 years 278 (15.99%), 50-59 years 488 (28.06%), 60-69 years 226 (13%), and above 70 years 122 (7%), whereas mean age 44.34 and the standard deviation 17.247 Figure-1. We also calculate the distribution of dysphonic disorders according to sex. Table-2. Distribution of laryngeal pathology among patient, non-specific chronic laryngitis was 1015 (58.37%), dysphonia without structural change or functional or MTD 417 (23.98%), malignant growth 90 (5.17%), vocal cord polyp 66 (3.79%), vocal cord nodule 55 (3.16%), vocal cord paralysis 35 (2.01%), laryngeal candidiasis 26 (1.49%), reienke's edema 22 (1.27%), vocal cord leukoplakia 04 (0.23%), tubercular laryngitis 04 (0.23%), vocal cord papilloma 02 (0.12%), vocal cord ulcer 02 (0.12%), and cyst on epiglottis 01 (0.6%).Table-1. Personal history exhibited smoker was 911 (52.39%), non-smoker 828 (47.61%), diabetic 796 (45.77%), non-diabetic 943 (54.23%), hypertensive 785 (45.14%), non-hypertensive 954 (54.86%), betel leaf and nut chewer 249 (14.32%), non-chewer 1490 (85.68%), history of previous radiotherapy 19(1.09%), no radiotherapy 1720 (98.91%), previous radioiodine ablation for thyroid carcinoma 13 (0.75%), no ablation 1726 (99.25%), alcoholic 11 (0.63%), and non-alcoholic 1728 (99.37%). Figure-2 Predisposing factor presented voice abuser was 469 (26.97%), reflux related 44 (2.53%), allergic manifestation 35 (2.01%), obesity 17 (0.98%), combined 315 (18.11%) and unknown 859 (49.40%). Figure-2 We calculate the distribution of dysphonic patient's risk factor related to personal history and predisposing factor. Table-3. Occupational status showed industrial worker was 477 (27.43%), teacher 359 (20.64%), singer 151 (8.68%), mothers of young children 128 (7.36%), shopkeeper 127(7.30%), receptionist 123 (7.07%), councilor 121 (6.97%), house wife 117 (6.73%), hawker 65 (3.74%), student 33 (1.90%), leader 31 (1.78%), and retirees 07 (0.40%). Figure-1 Residence of the patient revealed slum dwellers was 528 (30.36%), suburban 519 (29.85%), rural 487 (28%), and urban 205 (11.79%). Figure-2 Presenting features displayed hoarse, rough, and breathy voice was 1721 (99.14%), an inability to raise the voice (reduced loudness) 1652 (94.99%), an increased effort to talking (tiring to talk) 1582 (90.97%), an inability to control the voice (breaking of speech) 606 (34.85%), reduced ability to communicate effectively 539 (30.99%), throat related symptoms (soreness, discomfort and burning sensation) 204 (11.73%), difficulty in singing 151 (8.68%), difficulty in respiration 139 (7.99%), cough and frequent clearing of throat 121 (6.96%) and neck mass 36 (2.07%)Figure-2. Investigations performed l/L was 215 (12.36%), FOL 237 (13.63%), and RTL 1739 (100%).Figure-3 Disease pattern manifested non-neoplastic or non-structural benign lesion was 1497 (86.08%), and suspected malignancy 06 (0.35%), neoplastic or structural benign lesion was 146 (8.4%), and malignant growth 90 (5.17%). Figure-3 Treatment option conveyed medical was 1512 (86.94%), and surgical 227 (13.06%). Figure-3

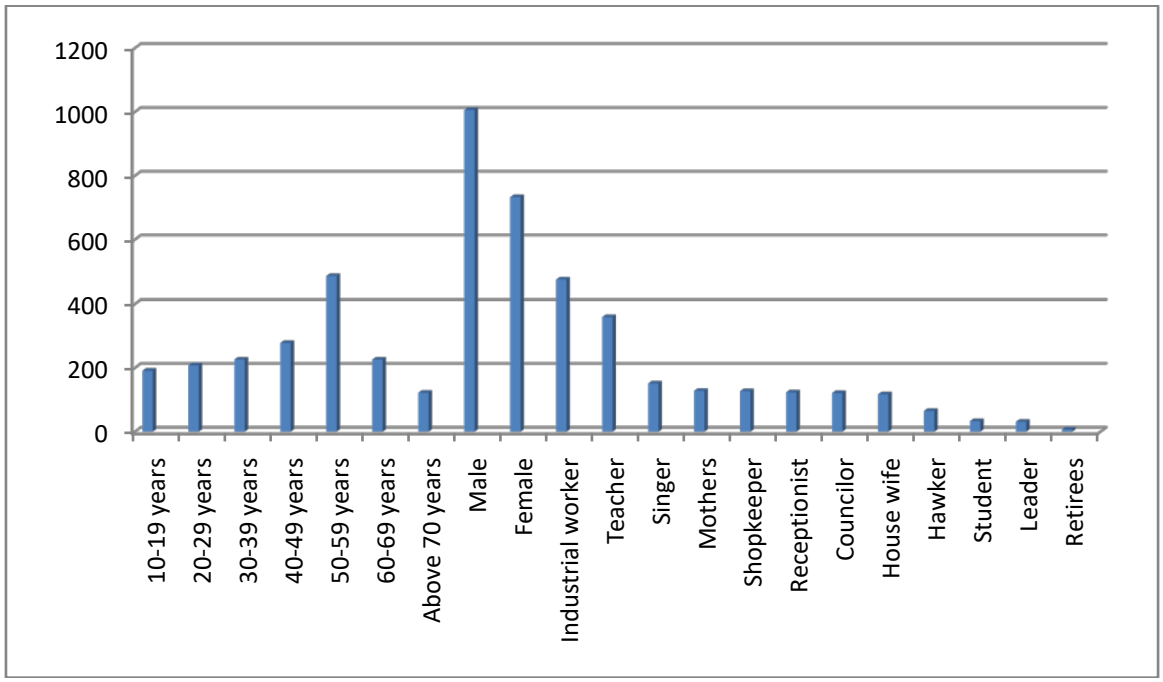

Figure-1: Age, Sex and Occupation.

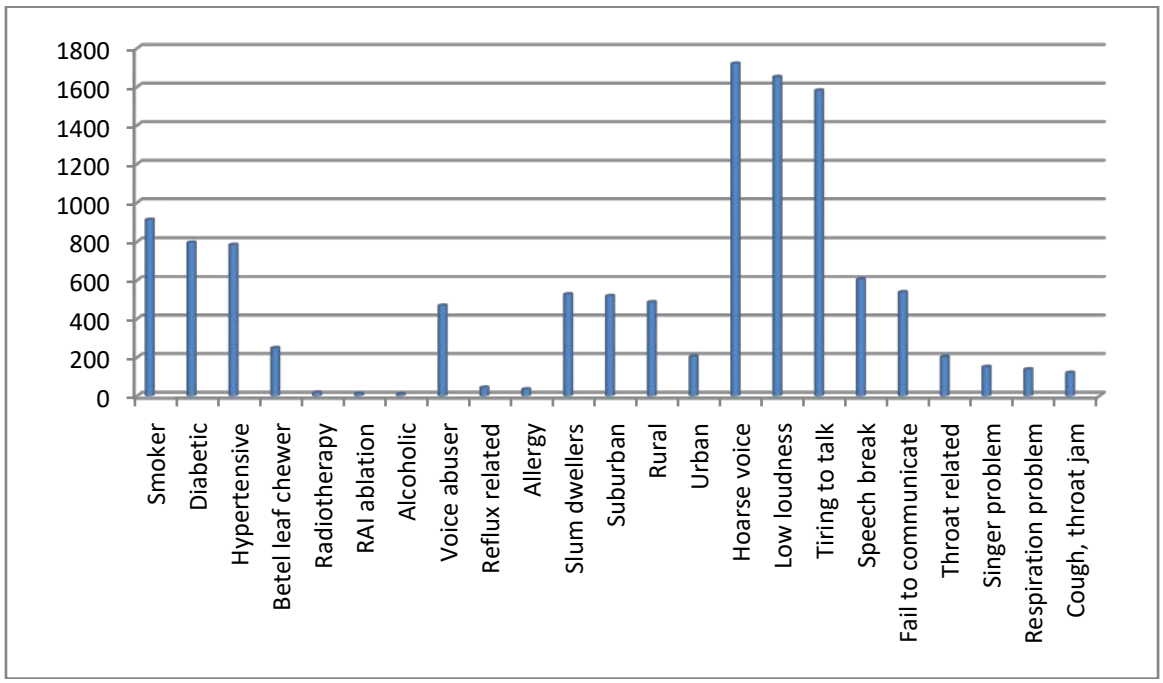

Figure-2: Personal history, predisposing factor, residence and well known presenting feature.

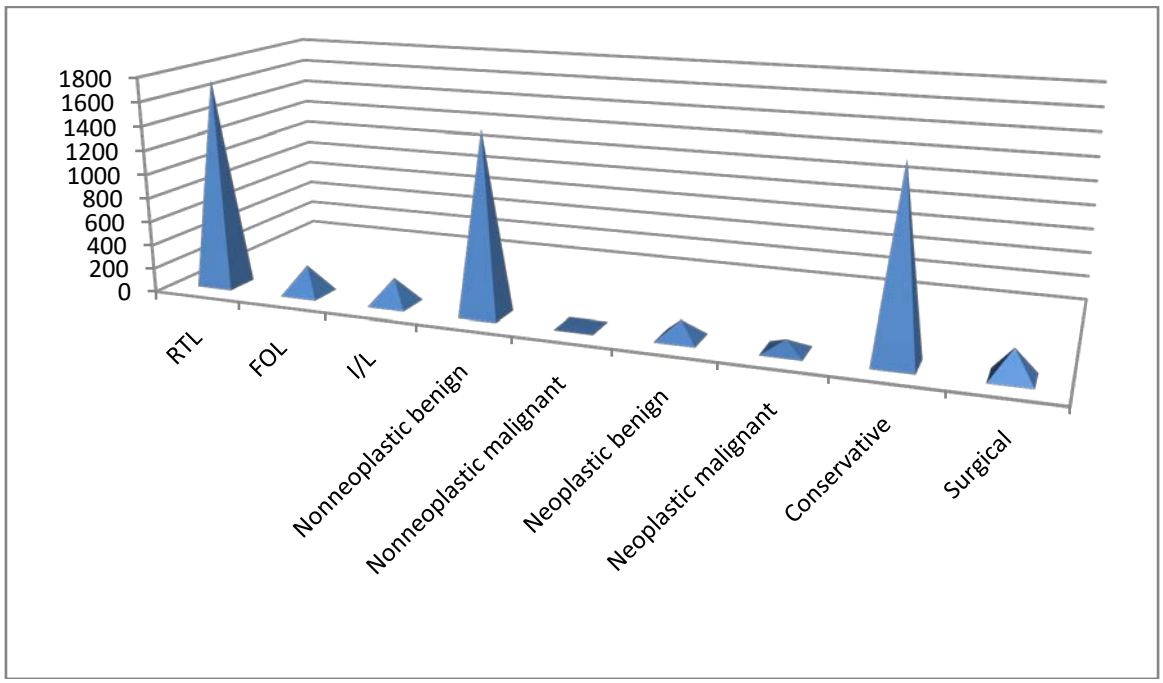

Figure-3: Investigation, disease pattern and treatment option of dysphonia.

Table-1: Distribution of laryngeal disorder due to Dysphonia.

Serial Number	Laryngeal Disorders	Patient in Govt. hospital	Patient in Private hospital	Total patient	Percentage
1	Non-specific chronic laryngitis	420	595	1015	58.37%
2	Dysphonia without structural change/Functional/MTD	230	187	417	23.98%
3	Malignant growth	69	21	90	5.17%
4	Vocal cord polyp	61	05	66	3.79%
5	Vocal cord nodule	38	17	55	3.16%
6	Vocal cord paralysis	34	01	35	2.01%
7	Candidiasis	09	17	26	1.49%
8	Reinke's edema	21	01	22	1.27%
9	Vocal cord leukoplakia	03	01	04	0.23%
10	Laryngeal TB	03	01	04	0.23%
11	Vocal cord Papilloma	02	00	02	0.12%
12	Vocal cord ulcer	02	00	02	0.12%
13	Cyst on epiglottis	01	00	01	0.06%
T0tal		893	846	1739	100%

Table-2: Distribution of laryngeal disorders according to sex.

Serial	Laryngeal disorders	Male	Percentage	Female	Percentage
1	Chronic laryngitis (1015)	580	57.14%	435	42.86%
2	Functional/MTD (417)	238	57.07%	179	42.93%
3	Malignancy (90)	88	97.78%	02	2.22%
4	Vocal cord polyp (66)	38	57.58%	28	42.42%
5	Vocal nodule (55)	15	27.27%	40	72.73%
6	Vocal paralysis (35)	14	40%	21	60%
7	Candidiasis (26)	05	19.23%	21	80.77%
8	Reinke's edema (22)	18	81.82%	04	18.18%
9	Leukoplakia (04)	03	75%	01	25%
10	TB laryngitis	03	75%	01	25%
11	Vocal Papilloma (02)	02	100%	00	00%
12	Vocal Ulcer (02)	02	100%	00	00%
13	Cyst (01)	00	00%	01	100%
Total	1739	1006	57.85%	733	42.15%

Table-3: Distribution of risk factor of laryngeal disorder according to personal history and predisposing factor.

Serial	No. of patient	Laryngeal disorders	Smoking	Voice abuser	Alcohol	Betel leaf	Allergic disorder	Reflux related	Other
1	1015	Chronic laryngitis	494	302	00	190	20	09	00
2	417	Functional	252	102	00	32	12	19	00
3	90	Malignancy	88	00	00	02	00	00	00
4	66	Vocal polyp	30	18	00	10	00	08	00
5	55	Vocal nodule	10	35	05	00	00	05	00
6	35	Vocal paralysis	10	00	05	00	00	00	20
7	26	Candidiasis	00	05	00	15	03	03	00
8	22	Reinke's edema	17	04	01	00	00	00	00
9	04	Leukoplakia	03	01	00	00	00	00	00
10	04	TB Laryngitis	03	01	00	00	00	00	00
11	02	Papilloma	02	00	00	00	00	00	00
12	02	Ulcer	02	00	00	00	00	00	00
13	01	cyst	00	01	00	00	00	00	00
Total	1739		911	469	11	249	35	44	20
	100%		52.39%	26.97%	0.63%	14.32%	2.01%	2.53%	1.15%

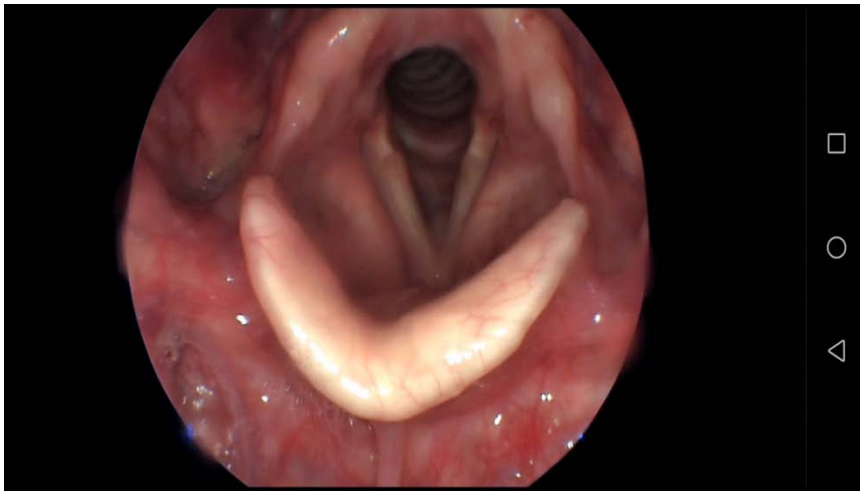

Figure-4: Normal Larynx.

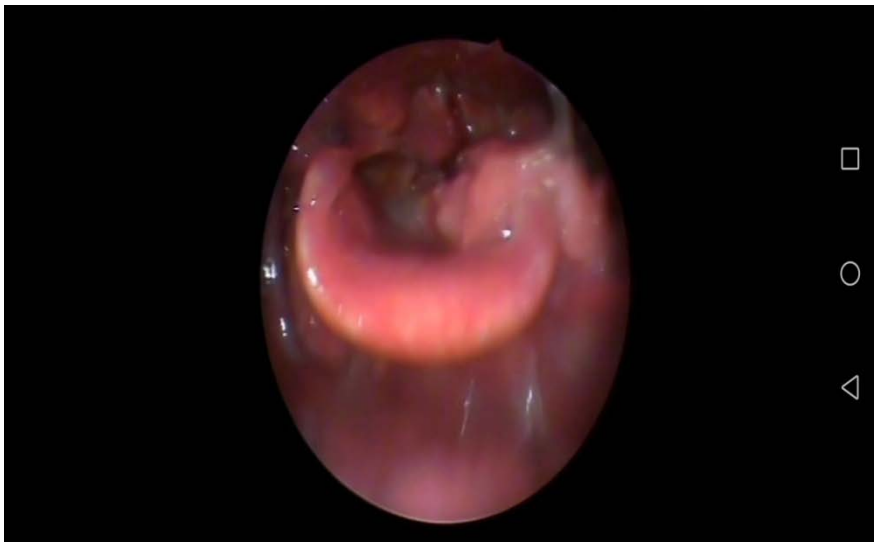

Figure-5: Supraglottic huge growth.

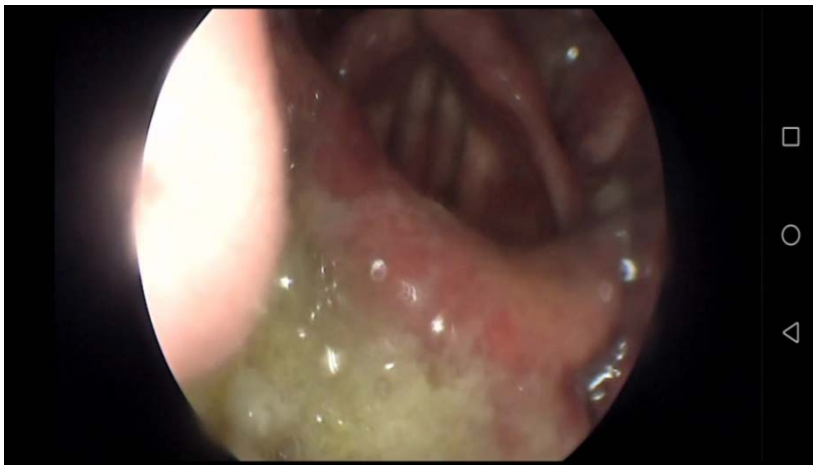

Figure-6: Growth on lingual surface of epiglottis.

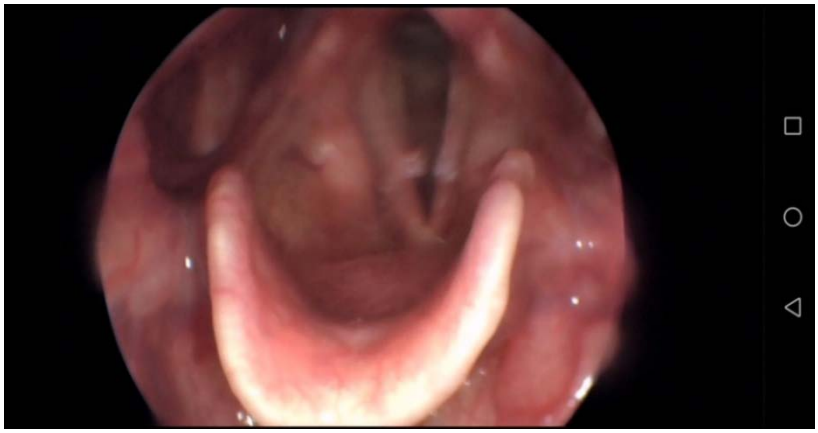

Figure-7: Vocal cord nodule.

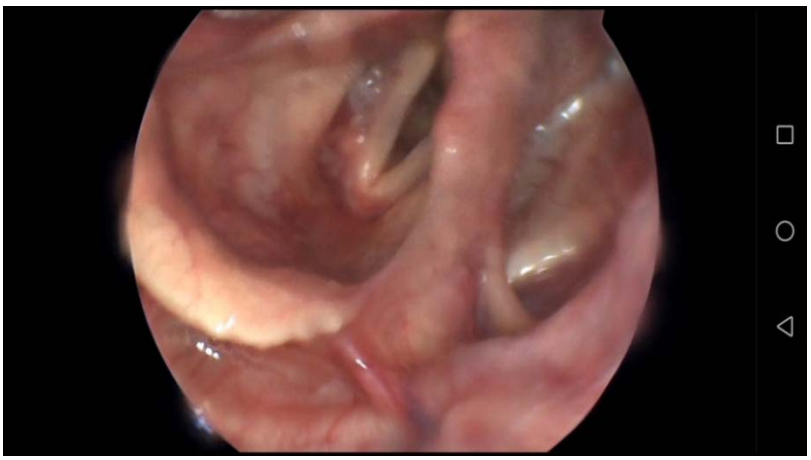

Figure-8: Functional dysphonia.

IV. Discussion

Distribution of laryngeal pathology due to symptoms of dysphonia among our patient was seventeen hundreds thirty nine. Incidence of dysphonia was 1.16% among outpatient department and the yearly prevalence of 33.33 % in our study consistent with Roy et al. series, showed 30% prevalence rate [21].

In the present study, non-specific chronic laryngitis was the most common disease-producing dysphonia 1015 (58.37%) kept up by Khammas AH, Abodamen, and Kataria et al. series, reported the highest occurrence of chronic laryngitis accordingly 19.11%, 27.91% and 20.55% [22] [23] [24]. The patient was mostly male, 57.14 %, also supported by Goswami S et al. showed 62% patient was male [25]. About predisposing factors, allergic manifestation was the second most causes in our results 2.01% held up by Hamdan AL et al. also reported 15-25% singers to have dysphonia with allergic rhinitis [26]. Reflux originated

chronic laryngitis was 2.53% in our study against Jacob et al. showed 25% patient of chronic laryngitis was associated with reflux-related [27].

The second most common cause of dysphonia was functional or MTD in our work. Out of 417 (23.98%) MTD patients, the male was 238 (57.07%), and the female 179 (42.93%), opposite to Altman KW et al. series, they observed 60% were female and 40% male [15]. Personal history revealed in our work, previous radiotherapy was 19 (1.09%) and radioiodine ablation 13(0.75%) who suffered from anxiety, tension and mood disorder always about their future handicap supported by House A. et al. study showed one-third of functional dysphonic patients abide by anxiety and mood disorder [28].

The third most common cause malignant lesion was 5.17% in our paper persistent with Khammas AH and Kataria et al. study, reported third common cause was malignancy accordingly 16.9% and 11.67% [22] [24]. Kiakojoury K et al. also supported our research, showed laryngeal cancer caused dysphonia was 2.5% [29]. Smoking is the prime risk factor of our study 52.39%, supported by all other studies like Goswami S and Khammas AH et al. reported accordingly 100% and 53.68% [25] [22].

Vocal cord polyp was 3.79% dysphonia in our series against Goswami S et al. paper, showed 16.9% case [25]. Sex distribution in our study the male was 57.58%, and the female was 42.42% near to Singh R et al. research revealed male, the female ratio was 2:1[30]. Vocal cord nodule was 55 (3.16%) in the present study isn't compatible with Babu VS et al. series, showed vocal nodule 11.95% [31]. The female was 72.73%, and the male 27.27% kept up by Goswami S et al. reported 67.86% was female, and 32.14% was male [25].

Vocal cord paralysis was 35 (2.01%) in our research consistent with Roy D et al. work, Presented a 2.9% case was paralysis [32]. Gender distribution displayed the female was 20 (58.82%), and the male 14 (41.18%)-, due to female thyroidectomy was 08 times more than male in our hospitals held up by Ko HC et al. series [33].

In our paper, 26 (1.49%) was a fungal infection in which the female was 21 (80.77%) and the male 05 (19.25%). It is associated with an immuno-compromised patients like post-irradiated, radioiodine ablation, frequently received antibiotics. In our work post-irradiated 19 (1.09%) and radioiodine ablation 13 (0.75%) supported by Vrabec DP's study [13].

Reinke's edema was in our work 21 (1.27%) held up by Singh R et al. reported 2% whereas Goswami S et al. against our study showed 26.7% [30] [25]. Smoking (52.39%) was the main risk factor for Reinke's edema in our research kept up by Ballenger JJ. series [34].

Vocal cord leukoplakia is the premalignant condition. Among 04 (0.23%), the male was 03(75%), and the female 01 (25%) in this work. The risk factor for it in our report was smoking (52.39%) and voice abuse (26.97%) kept up by Sing R et al. series [30].

Laryngeal TB is secondary to pulmonary TB. Smoking (52.39%) is another risk factor held up by Chopra H et al. paper [35], reported 03 (4.48%) patients of laryngeal TB.

In our study, only 02 (0.12%) cases of adult papilloma whereas Goswami S showed JRRP patient was 11 (1.4%) [25].

The ulcer may be a premalignant condition or due to TB and Syphilis supported by Bhat VK et al. series [36].

Cyst of the epiglottis is a rare condition. Only one female patient found epiglottis cyst which was mucous retention cyst [2]

V. Conclusion

Dysphonia is one of the prime symptoms of the laryngeal disorder. The rigid RTL is available for accurate and safe examination, and assessment of the disease condition. Proper treatment and management can be reduced the morbidity and mortality rate of the patient suffering from various laryngeal diseases that causes dysphonia.

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Ethical Approval

The Institutional Review Committee approved the study, headed by the Principal of the Medical College, chief editor of the Journal of comilla medical college teachers association is secretary and all head of the department was member named Journal Review Ethics Committee.

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Managing Shingles (HZ) in Elderly with Topical Application of Acyclovir 5 Mg and Increasing Immunity with Matily Herbal Drink - A Case Study

By John T. Eapen

Introduction- Varicella zoster virus (VZV) causes chickenpox, a self-limited disease with disseminated skin lesions that occurs mostly in childhood. It usually persists symtomatically in the dorsal root ganglia of anyone who has had chickenpox. It reactivates from its dormant state and travel along the sensory nerve, causing vesicular lesions in the dermatome supplied by that nerve in about 25% of people who had chickenpox in their childhood. These lesions, known as Herpes zoster or shingles and it causes a painful eruption of a rash, usually unilaterally. It occurs more frequently in older adults and immunocompromised individuals (1). HZ afflicts millions of older adults worldwide and causes significant suffering because of acute and chronic pain, or postherpetic neuralgia (PHN) (2).

It is believed that the potential risk factors for HZ are aging and suppression of cellular immunity (1,2,3).

They treat HZ with topical application of Acyclovir 5% cream. In severe cases, they prescribe Acyclovir 800 mg 5 times daily for 7 to 10 days and, they recommend taking plenty of water along with medication (4). Therefore, it is for patients with normal cardiac and kidney function.

GJMR-F Classification: NLMC Code: QW 540

Managing Shingles (HZ) in Elderly with Topical Application of Acyclovir 5 Mg and Increasing Immunity with Matily Herbal Drink - A Case Study

John T. Eapen

I. Introduction

Varicella zoster virus (VZV) causes chickenpox, a self-limited disease with disseminated skin lesions that occurs mostly in childhood. It usually persists symtomatically in the dorsal root ganglia of anyone who has had chickenpox. It reactivates from its dormant state and travel along the sensory nerve, causing vesicular lesions in the dermatome supplied by that nerve in about 25% of people who had chickenpox in their childhood. These lesions, known as Herpes zoster or shingles and it causes a painful eruption of a rash, usually unilaterally. It occurs more frequently in older adults and immunocompromised individuals (1). HZ afflicts millions of older adults worldwide and causes significant suffering because of acute and chronic pain, or postherpetic neuralgia (PHN) (2).

It is believed that the potential risk factors for HZ are aging and suppression of cellular immunity (1,2,3).

They treat HZ with topical application of Acyclovir 5% cream. In severe cases, they prescribe Acyclovir 800 mg 5 times daily for 7 to 10 days and, they recommend taking plenty of water along with medication (4). Therefore, it is for patients with normal cardiac and kidney function.

In this communication, we want to present a case of an older adult with HZ who managed with only topical acyclovir 5%. He could not take Acyclovir 800mg orally because he had to limit his water intake to just 1 to 1.5 liter because of his medication for the heart. The only option available to the patient was to increase his cellular immunity with Matily herbal drink (5).

II. Case Study

An elderly male, 64 years old with a history of Congestive Heart Failure (CHF), was resting at home and could not move around because of COVID 19 lockdown. He was a diabetic patient for nine years. He took medication for diabetes in the first month when the doctor diagnosed him as a diabetic patient. The medication increased his appetite, and therefore he stopped it. He manages his hyperglycemia with diet and exercise. His diet comprises natural home-cooked food with no preservatives or anti-caking agents. He used to walk at least 2 km a day, and all these kept his blood sugar under control.

During the lockdown period, the patient had a recurrence of CHF and was resting at home. Lockdown restricted his physical activity of walking. After a few weeks, the patient had HZ in the thoracic region.

The dermatologist recommended- acyclovir 5% cream for topical application and oral intake of acyclovir 800 mg 5 times daily for 7 to 10 days. Oral intake of acyclovir recommends drinking plenty of water. In the present case study, the Cardiologist had recommended not to take over 1 to 1.5 liter in a day. During the lockdown period, the combined consultation of a cardiologist and dermatologist was not available in the town where he was staying.

Under the above condition, the patient increased his cellular immunity with Matily herbal he had made two years ago to control his hyperglycemia and hyperlipidemia. We give elsewhere the details of the drink (5).

III. Results

The combination of topical application of Acyclovir 5 mg and intake of Matily Herbal drink gave relief to the patient. The pain subsided, and the lesions were in the healing process. There were about five or six post herpatic neiralgia which gave severe pain in the beginning. Later on, the pain subsided and all were healed. Though major lesions healed in a week's time, the PHN took nearly one and a half month for complete healing. Thus, combination of topical application of Acicyclovir 5 mg and Matily Herbal Drink helped in the recovery of shingles.

IV. Discussion

Herpes Zoster (HZ), known as shingles, results from reactivation of latent varicella-zoster virus and occurs more frequently in older adults and in immunocompromised individuals (1). Aging and decreased cellular immunity are the potential risk factors. Vaccination is available for preventing HZ. However, the vaccination has a life of only 7years.

Against such a backdrop, we may prefer the present method as it increases cellular immunity with natural products. In the present case studies, hyperglycemia resulting from oxidative stress was a risk

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factor. Reduced physical activity because of CHF and lockdown may have caused this. Hyperglycemia produces free radicals in the body and increases the demand for antioxidants in the body. When adequate antioxidants are not present the cellular immunity alone cannot eliminate free radicals. Free radical production in the body speeds up aging. All these may contribute to reduced cellular immunity.

Matily drink has both hypoglycemic and hyperlipidemia properties (5). It is rich in polyphenols which act as antioxidants. It increases bioavailability when it ferments a few hours at room temperature. We describe elsewhere the contributions of all the ingredients in the concoction (5). Thus Matily Herbal Drink may have increased cellular immunity, and we can undoubtfully consider it as a secondary treatment method.

In the ongoing discussion we want to point that Matily Herbal Drink may also contribute to the primary treatment of the viral disease because the ingredients in the drink contain ani-viral constituents in them.

Pudina belongs to Mint Family (Labiatae) has ani-viral properties (6). Fresh ginger has anti-viral properties as reported (7). Similarly, curry leaves have many medicinal properties (8).

The author holds a hypothesis that any plant susceptible to virus attack in their vegetative stage develops anti-viral substances in their fruit and seeds to ward off virus attack and continue life on earth. Example - Tomato plants are prone to viral attack (9) but their fruits and seeds contain anti-viral constituents in them (10). Viruses affect citrus trees (11) but the lemon fruits have excellent anti-viral properties (12). We well know it controls influenza virus. Similarly, virus attack okra cultivation in India (13). However, references to any anti-viral compounds in okra is not available. It reports the immunomodulatory effect of okra (14) and beneficial effects of bioactive compounds in them (15). We believe that the mucilage in okra pods may have anti-viral action and protect the seeds. Its action could be mainly through physico-chemical properties of the mucilage. The mucilage reduces surface tension of water (16) just like soap in water. It is an emulsifier (17). It promotes flocculation (18). Mucilage is viscous depending on the pH and temperature. Under normal circumstances the mucilage in them may prevent the virus particles attaching with host cells. Thus mucilage in the pods may protect the growing seeds in them. Thus mucilage in the okra pods may have anti-viral protection mainly by their physical properties.

In the present case study, the patient never had a common cold in the last two years. Perhaps the anti-viral constituents in the herbal drink had some protective effect on the patient.

We want to conclude with following notes.

1) Given all the properties of the constituents in the herbal drink, it may have some primary action on the HZ which warrants further study.
2) Since Matily Herbal Drink is slightly viscous depending on the quantity of lemon juice used, it is worth studying the effect of the drink in preventing COVID 19 virus attaching with ACE receptors in the human throat region. Incidentally, the patient mentioned here developed slight throat pain after passing through a containment zone for some urgent work. He felt slight throat pain and tiredness. Then after returning home, he sipped the above drink and found complete relief after taking rest for a few hours.

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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.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

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

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