International Journal of Otorhinolaryngology and Head and Neck Surgery
Shakeel M et al. Int J Otorhinolaryngol Head Neck Surg. 2017 Apr;3(2):414-418
http://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937

Case Report

DOI: http://dx.doi.org/10.18203/issn.2454-5929.ijohns20170542

Non responding Ludwig's angina due to starvation and PEM: review of literature and a case report

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Received: 01 January 2017
Revised: 07 February 2017
Accepted: 13 February 2017

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ABSTRACT

Relationship between starvation and immunosuppression was initially suggested on the basis of increased rate of infectious disease during famine. Latter on this was confirmed by thorough studies of immune response in starved and malnourished patients. There are numerous defense mechanisms to protect human host from infection. Starvation leads to immunosuppression due to its damaging effects over these defense mechanisms, thereby increasing chance of opportunistic infections e.g. Ludwig's angina. Not only this, it also alters the natural course and drug response of disease. Ludwig's angina is infection of submandibular space which lies between mucous membrane of floor of mouth on one side and superficial layer of deep cervical fascia on other. It is surgical emergency that is potentially life threatening unless early recognized and aggressively treated. Although most reported cases follow an odontogenic infection, it can occur in persons with no co-morbid disease and individuals with starvation and protein energy malnutrition also are at increased risk of developing it due to immunosuppression. Here we report a case of female who was starved for 14 days as she fell in well and presented with Ludwig's angina, resistant to standard treatment protocol. The aim of this paper was to review literature supporting relationship between starvation and immunosuppression and present a case of starved female presenting with Ludwig's angina resistant to treatment. We emphasize about the proper history tacking after counselling in cases resistant to treatment. It is important to assess the nutritional status of the patient in every case of Ludwig's angina. This is important because Ludwig's angina associated with other etiologies also develop restricted mouth opening thereby decreasing oral intake which further leads to nutritional deficiency and PEM.

Keywords: Ludwig's angina, Starvation, Immunosuppression

INTRODUCTION

Humans are protected from intrusion of pathogens by their strong defense mechanisms. These defense mechanisms, which protect human host from infections, are classified into innate immunity and acquired immunity. Innate immunity serves to protect the host without prior exposure to an infectious agent. Resistance acquired by an individual during life, either actively by infection, vaccination or passively by transfer of antibody, lymphocytes from an immune donor is known as acquired immunity.

Starvation or protein energy malnutrition leads to immunosuppression due to its damaging effects over defense mechanisms.[1-3] Cells of immune system are dependent on presence of various cofactors and micro-nutrients for their growth and normal function. So the extent of damaging effect over the cells of defense mechanism depends on the rate of cell proliferation, amount and rate of protein synthesis and role of

individual nutrients in metabolic pathways. The lymphoid tissues are most vulnerable of defense mechanism.[4]

Even deprivation of single nutrient, may lead to changes in absorption of other substance. Starvation leads to shortage of multiple micronutrients, vitamins, proteins, resulting in hampering of proliferation of rapidly dividing cells of lymphoid tissue leading to immunosuppression. Not only this there is also increased adherence of bacteria to respiratory and buccal epithelial cells in starved and malnourished persons, thereby increasing the risk of opportunistic infections in nutritional deficiency.[5] Nutritional deficiency also leads to changes in biological gradient, natural course and drug response of infection.

Ludwig's angina is surgical emergency that is potentially life threatening unless early recognized and aggressively treated. It is a rapidly progressive bilateral cellulitis of submandibular space associated with elevation and posterior displacement of tongue. Though it can occur in persons with no comorbid disease, individuals with decreased immunity are at increased risk of developing it.

Here we present a case of 40 years female who was starved for 14 days, developed protein energy malnutrition and presented with non-responding Ludwig's angina. Our case report and extensive review of literature highlights the fact that starvation not only leads to immunosuppression and increases chance of opportunistic infections, but also leads to increased virulence of pathogens and alters the natural course and drug response of the disease. Therefore such a surgical emergency should be treated by multiple approaches for immediate response.

CASE REPORT

A 40 years female, presented to our ENT OPD with difficulty in opening mouth and swallowing, which was sudden in onset and gradually progressive, for last 3-4 days. There was no history of dental extraction or trauma. She was getting injectables from local practitioner but no documents were available for the same. Though this could be elicited from the attendant that IV fluids and injectable antibiotics was given by the local practitioner. On examination, patient was febrile and there was generalized swelling present over the bilateral sub-mandibular region and submental region, swelling was tender and woody hard. Mouth opening was restricted to 1 finger only. Oral hygiene was satisfactory as she was using mouth gargle for last 2 days. Dental examination was within normal limit and there were no signs of dehydration. On routine hematological investigation except for low serum potassium level rest investigations were within normal limits. She was diagnosed as case of Ludwig's angina.

Incision and drainage of submandibular swelling was performed and drained out pus was sent for culture and sensitivity, which later on demonstrated the presence of *Staphylococcus aureus* sensitive to amikacin, ceftriaxone, levofloxacin and clindamycin. Injectable ceftriaxone, amikacin and metronidazole were empirically started, along with daily dressing of surgical wound. Even 48 hours after the start of treatment, pus formation, sloughing and inflammation did not decreased in amount. Since most of cases of Ludwigs angina respond to surgical intervention and empirical drug therapy, for revising the treatment strategy, once again detailed history was taken, and then we got an interesting fact of fall in well 16 days back. She remained inside the well for 14 days. She used to feed herself on herbs and wood inside the well. She was rescued after 14 days. She had the newspaper cutting in which this incident was published. She had not disclosed this incident initially as she did not wanted undue attention and suspicion which she was facing since then. According to patient and her attendants she had good health prior to the incident, though patient was not aware of her exact weight prior to incident as she was from poor socioeconomic background and had never got her weight measured. During this period patient lost significant weight and musculature, as told by the attendants, and as could be elicited by the history of loosening of cloths.

Considering above history and fact of starvation of 2 weeks and culture and sensitivity report supporting our empirical drug treatment, she was re-diagnosed as non-responding Ludwig's angina with protein energy malnutrition. So her serum albumin level was done which was 2.7 g/dl, which is below normal range. Medicine reference was sought and she was advised 1 unit albumin infusion once a day for 3 days. A dietician reference was also sought to provide therapeutic diet chart. Therapeutic diet was advised and started. Same injectables in same dose and schedule, as was given earlier in empirical drug therapy, were continued along with daily dressing. She was continued on same treatment for 3 days and responded well to treatment, seen clinically as amount of pus and sloughing decreased and wellbeing of patient also improved. After this she left against medical advice due to financial reasons.

DISCUSSION

Ludwig's angina

Ludwig's angina is infection of submandibular space which lies between mucous membrane of floor of mouth on one side and superficial layer of deep cervical fascia on other. It is divided by mylohyoid muscle into 2 compartments-sublingual compartment above the mylohyoid and submaxillary and submental compartment below the mylohyoid.

Ludwig's angina is named after Wilhelm Friedrich von Ludwig, a German physician, who first described this condition.[6] Ludwig's angina is known by many alternative names, including cynanche, carbuculus gangraenosus, angina maligna, morbus strangularis, and

garotillo. It is potentially life threatening cellulitis or connective tissue infection of neck and floor of mouth. There is progressive submandibular swelling with elevation and posterior displacement of the tongue.[7] About 70% of cases are due to odontogenic infections. Lower second molar is most common site of source of infection for Ludwig's angina but lower third molar is also commonly involved route of infection.[8]Other cause for infection includes mandible fracture, salivary calculi, oral mucosal injury.

Our patient fed on herbs and woods for 14 days, resulting in protein energy malnutrition. During this period oral hygiene was maintained by the herbs intake, which keeps on cleaning the oral cavity, as in animals. After coming out of well protein energy malnutrition was not checked by the therapeutic diet which further lead to immunosuppression and infection supervened. So not only the causative factors discussed above, but also the protein energy malnutrition may lead to opportunistic infections causing Ludwig's angina. These infections may remain/become resistant to treatment if protein energy malnutrition is not corrected by therapeutic diet.

The most commonly cultured organisms include *Staphylococcus, Streptococcus*, and *Bacteroides* species.[9] Immunocompromised patients are commonly infected with an atypical organism, such as *Pseudomonas, Escherichia coli, Candida,* or *Clostridium.*[10] Individuals with human immunodeficiency virus, diabetes mellitus, malnutrition, aplastic anemia and alcoholism are at increased risk, though in majority of patients there is no co-morbid disease. Smoking and poor oral hygiene predispose to development of Ludwig's angina.[11]

Symptoms of Ludwig's angina includes general symptoms such as fever, weakness, malaise. Oedema of submandibular region and neck results in trismus and pain during swallowing. With progressive oedema, upper airway obstruction occurs resulting in respiratory distress. Head and neck examination reveals submandibular swelling which is tense and tender. Structures in floor of mouth are swollen and tongue appears to be pushed up and back. Significant respiratory obstruction may result in tachypnoea or stridor. If not treated; infection may spread to parapharyngeal, retropharyngeal space and mediastinum. Septicemia may occur as with any bacterial infection.

CT scan and MRI are useful in assessment of drainable collection, extent of tissue infection or necrosis and to guide the approach of surgical intervention. According to a study drainable collection can be identified with accuracy of 89%, sensitivity of 95% and specificity of 80% by a combined approach of clinical evaluation and CT findings.[12] USG is reliable, cost effective modality to differentiate cellulitis related edemas from abscess collection.[13] Spread of infection to mediastinum can be confirmed on X-ray chest.

Our patient fed on herbs and woods for 14 days, resulting in protein energy malnutrition which was not checked by the therapeutic diet after coming out of well which lead to immunosuppression and opportunistic infection supervened. Furthermore this infection under the influence of PEM became resistant to drug treatment due to increased virulence of pathogens and decreased host defense mechanism. Response became evident, with same treatment protocol, once the protein energy malnutrition was targeted with albumin infusion and therapeutic diet.

Immunity and virulence of pathogens in relation to starvation

The relationship between immunosuppression and starvation was initially suggested on the basis of increased rate of infectious disease during famine.[14] Latter on this was confirmed by thorough studies of immune response in starved and malnourished patients.[2,4,15] Depressed immune response in starved persons enhances the risk and severity of infection. The documentation of adverse effects of starvation on morbidity and mortality is presented in several epidemiological studies.[16] Protein and protein-energy malnutrition in children are commonly associated with an increased incidence of mucosal infections and diarrhea, suggesting a malnutrition-induced defect in the mechanisms for protection of mucosal surfaces.

Anatomical changes in lymphoid tissues due to malnutrition have been described long time back. Thymus has been termed as sensitive barometer of malnutrition.[17] Changes in thymus due to malnutrition includes decreased size and weight, loss of corticomedullary differentiation and lymphoid cells decrease in number. Reduced cell mediated immunity is due to reduction in mature fully differentiated T lymphocytes which in turn is due to reduction in serum thymic factor activity in malnutrition.[18,19] The ratio of CD4+:CD8+ is also significantly decreased in malnutrition.[20] There is reduction in number of antibody producing cell and amount of immunoglobulin secreted.[21]

Role of leptin

Leptin is an adipocyte derived hormone and has cytokine like function and mediate the effect of starvation on immunity. Circulating levels of leptin are proportional to fat mass but may be lowered rapidly by fasting or increased by inflammatory mediators.[22-27] Impaired cell-mediated immunity and reduced levels of leptin are both features of low body weight in humans.[1,3,23] Leptin has a specific effect on T-lymphocyte responses, differentially regulating the proliferation of naive and memory T cells. Leptin increased Th1 and suppressed Th2 cytokine production. Administration of leptin to mice reversed the immunosuppressive effects of acute starvation. Leptin plays a role in linking nutritional status to cognate cellular immune function, and provide a molecular

mechanism to account for the immune dysfunction observed in starvation. A falling leptin concentration acts as a peripheral signal of starvation which serves to conserve energy in the face of limited reserves. Indeed, malnutrition predisposes to death from infectious diseases.[14]

Role of micronutrient

Several micronutrients play a key role in various metabolic pathway and cell functions. Except for Iron, Vitamin A and Zinc, isolated deficiencies of micronutrients are rare. However in malnutrition usually there are multiple nutrient deficiencies. Combined or individual deficiencies of micronutrients like Vitamin A, Vitamin B6, Vitamin C, Zinc, Copper, Iron etc may result in immunosuppression. Vitamin A is known as an anti-infective vitamin and can alter the morbidity and mortality of disease.[28] A study in Burkina faso showed major reduction of malaria morbidity with combined vitamin A and zinc supplementation in young adults.[29] T and B lymphocytes, natural killer cells and macrophages are dependent on carotenoids for their normal functioning.

Effect on phagocytosis

Complement components acts as opsonin, their concentration and activity are reduced during starvation and malnutrition hampering the phagocytosis.[30] Phagocytes can ingest particles normally but subsequent digestion of particles is reduced.

Effect on innate immune response

Innate immune response is decreased. There is decrease in lysozyme concentration. Adherence of bacteria to epithelial cells is increased.[5] These increases the chance of invasion and infection by bacteria. Virulence of the pathogens is also increased. Nutritional deficiency in starvation leads to changes in biological gradient, natural, and drug response of disease.

Clinical significance

Nutritional status should be accessed in all cases of infective etiology as poor nutritional status may result in non-responsiveness of infection to treatment.

CONCLUSION

Nutritional deprivation suppresses the immune function. Depressed immune response in starved persons enhances the risk and severity of infection. Deficiency of various micronutrients during starvation predisposes to immunosuppression. Leptin plays a role in linking nutritional status to cognate cellular immune function, and provide a molecular mechanism to account for the immune dysfunction observed in starvation. Once again while revising our knowledge and experience about Ludwig's angina- we emphasize about the proper history taking after counseling for non-responding Ludwig's angina even if our clinical diagnosis is confirmed and supported by investigations. As in our case we had to revise our history taking process, after the surgical procedure was performed, repeat history revealed interesting fact which patient was hiding intentionally. Furthermore as in our case of non-responding Ludwig's angina with PEM we recommend to assess the nutritional status of the patient in every case of Ludwig's angina .This is important because Ludwig's angina associated with other etiologies also develop restricted mouth opening thereby decreasing oral intake which further leads to nutritional deficiency and PEM.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Shakeel M, Gupta RK. Non responding Ludwig's angina due to starvation and PEM: review of literature and a case report. Int J Otorhinolaryngol Head Neck Surg 2017;3:414-8.