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Case Report

Strongyloides hyperinfection syndrome, *Cytomegalovirus enteritis* with viremia and recurrent gram-negative sepsis in a patient with recurrent thymoma: a case report

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ABSTRACT

Strongyloides stercoralis is an intestinal nematode which is endemic in tropical and subtropical countries. It may cause asymptomatic infections, mild eosinophilia or hyperinfection syndrome in the most severe form. We are reporting a case of Strongyloides hyperinfection syndrome in an immunosuppressed patient with recurrent thymoma and myasthenic crisis. This patient is a 51-year-old man with myasthenia gravis on long term pyridostigmine and prednisolone and mycophenolate. He presented with copious diarrhoea and was in septic shock. His blood and urine cultures grew Klebsiella pneumoniae and Pseudomonas aeruginosa. Oesophago-gastro-duodenoscopy (OGD scopy) and biopsy showed severe active duodenitis with strongyloidiasis and moderate active antral gastritis with strongyloidiasis. He was diagnosed to have Strongyloides hyperinfection and was treated with oral Ivermectin. He recovered well. He was subsequently diagnosed to have CMV enteritis with viraemia and was treated with intravenous Ganciclovir. Our case emphasizes the association of Strongyloides hyperinfection with superimposed CMV infection and gram-negative sepsis due to prolonged immunosuppression and autoimmunity in Thymoma patients. Recurrent thymoma and high-grade infiltrative thymoma often poses difficulty in the management of myasthenia patients. A high index of suspicion and aggressive treatment is paramount in approaching a patient with multiple risk factors of hyperinfection syndrome and autoimmunity. This case is reported in view of its rarity and significance regarding the multidisciplinary approach in decreasing morbidity and mortality in hyperinfection syndrome with an autoimmune background.

Keywords: Strongyloidiasis, Cytomegalovirus, Thymoma, Myasthenia gravis

INTRODUCTION

Thymic tumours are rare neoplasms that arise in the anterior mediastinum. Most of them have an indolent growth and good prognosis, but 7-30% of the patients will have a recurrence.[1] Thymoma is associated with immune dysregulation resulting in autoimmune disorders, most common being Myasthenia gravis.[2] Myasthenic symptoms persist even after thymectomy and about 80% of these patients require long term immunosuppression.[1] They are also at increased risk of multiple infections due to immunodeficiency, a consequence of immune dysregulation and long-term immunosuppressive therapy.

Strongyloides stercoralis, an intestinal nematode, is endemic in tropical and sub-tropical countries. Though the exact prevalence is unknown, an estimated 30-100 million people are affected worldwide.[3] Strongyloidiasis is often chronic and limited, but severe life-threatening disseminated infection and hyperinfection can occur in

some patients, especially if immunosuppressed. Risk factors for Strongyloides hyperinfection include alcoholism, disorders impairing gut motility, congenital immunodeficiency, malignancy, malnutrition, immunosuppression, haematopoietic stem cell transplantation, hypochlorhydria, lepromatous leprosy, viral infections such as human T-cell lymphotropic virus type-1 etc.[3,4] Opportunistic disseminated strongyloidiasis can cause increased morbidity and mortality in immunosuppressed patients. Cytomegalovirus (CMV) is one of the important opportunistic viral infections among immunosuppressed patients. Here, we report a case of a patient with recurrent thymoma, who had S. stercoralis hyperinfection, CMV enteritis with viraemia and gram-negative sepsis in the background of multiple myasthenic crises.

CASE REPORT

A 51-year-old gentleman, known case of thymoma, post thymectomy in 2001, who developed myasthenia gravis in 2011, with history of myasthenic crisis in 2015, and coronary artery disease post coronary artery bypass grafting in 2019, presented to us in October 2020 with complaints of voluminous diarrhoea. On examination, he was severely dehydrated and hypotensive with a blood pressure of 90/60 mm Hg. Routine lab parameters were noted for lymphopenia (10%), hyponatremia (127 mEq/^{L}), hypoproteinemia with albumin (3.0) and globulin (1.5). Stool sample for gastrointestinal molecular panel assay detected *Enteroinvasive* and *Enteroaggregative E. Coli*. Stool hanging drop test and clostridium difficile toxin assay were negative. Stool routine was notable for eggs and larval forms of Ancylostoma duodenale. He was dewormed with albendazole. Upper GI endoscopy was done for dysphagia. Duodenal biopsy and histopathological examination (Figures 1 a-d) proved severe active duodenitis with strongyloidiasis and moderate active antral gastritis with strongyloidiasis.

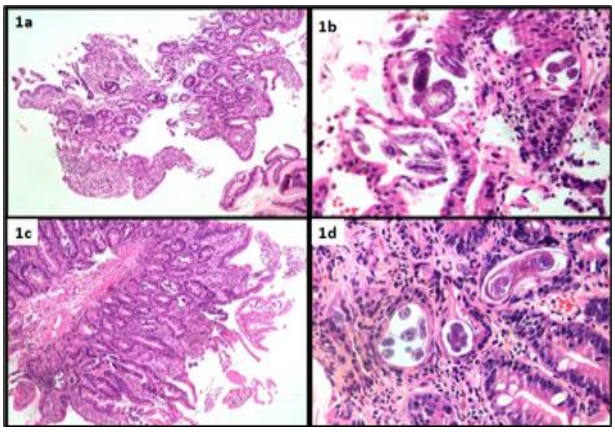

Figure 1: (a and b) Gastric mucosal biopsy with active inflammation and Strongyloides worms and eggs, 40X & 400X respectively; (c and d) duodenal mucosal biopsy with active inflammation and Strongyloides worms and eggs, 40X & 400X respectively, Hematoxylin & Eosin stain.

He was treated with oral Ivermectin. CT chest revealed mediastinal mass and hypoenhancing heterogenous nodule in the left lung, and it was suspicious for metastasis.

PET CT whole body was advised, but he was not willing. He was discharged on pyridostigmine and Mycophenolate mofetil (MMF), metronidazole and co-trimoxazole. Again, towards the end of October 2020, he presented to us with difficulty in passing urine, hesitancy, swelling of both legs and dysphagia.

On examination bilateral pitting pedal oedema was present. Initial investigations were noted for severe hyponatremia (115 mEq/l). CT pulmonary angiogram was done because of sudden onset hypoxia in the time of the COVID Pandemic. His COVID RT PCR was negative, and the CT did not show pulmonary embolism, but the thymoma had extended to the lateral border of the left atrium and left ventricle, infiltrating the adjacent pericardium and left superior pulmonary vein at its origin and encircling the oesophagus slightly with metastatic lymph nodal mass. It was categorized as stage 4b Masaoka Koga - staging system of thymoma stage.

Cardiothoracic surgeon reviewed and advised PET-CT whole body to assess tumour extension, but the patient was not willing. In November 2020, he presented with complaints of fever and burning micturition for two days. Upon examination, the patient was conscious oriented, febrile (100F), and hypotensive (90/50 mm Hg). His initial investigations revealed hyperglycemia (291mg/dl), serum ketoses (8.03), Leukocytosis (12660/mm^{3}) and hyponatremia (115meq/L).

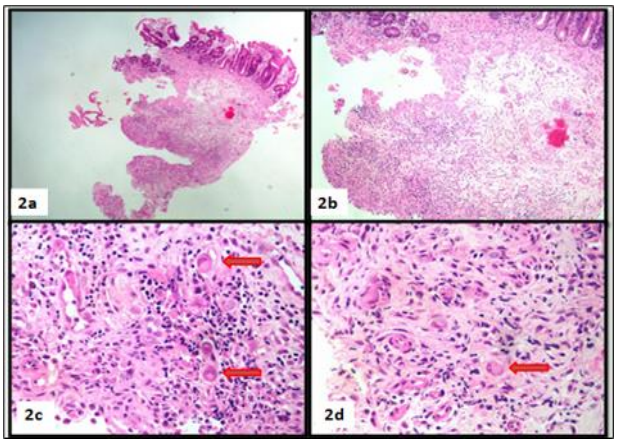

Figure 2: (a and b) Duodenal mucosal biopsy with ulceration and granulation tissue with proliferating blood vessels, 40X & 100X respectively; (c and d) intranuclear inclusion with "owl-eye" appearance in endothelial cells of the capillary wall, 40X &400X respectively, Hematoxylin & Eosin stain.

He was diagnosed to have *Pseudomonas* and *Klebsiella pneumoniae* urosepsis. He was started on Inj. Ceftazidime/ Avibactam 2.5g IV Q8H). In view of

recurrent infections, mycophenolate mofetil was stopped, and oral steroids were tapered down with the intent to discontinue. CT abdomen was done as the patient had melena and it revealed jejunal and ileal loops appearing hyperdense, hemorrhagic fluid seen in the distal ileal loop and caecum and ascending colon, prominent submucosal vessels are seen in the proximal jejunal loops in left hypochondrium in portal and venous phase suggestive of angiodysplasia.

Upper GI bleed was confirmed by endoscopy, and he underwent superior mesenteric artery embolization. Biopsy (Figure: 2a-d) revealed CMV inclusion bodies in the D2 segment. CMV PCR count was elevated, and hence he was started on IV Ganciclovir.

He had sudden onset myasthenic crisis and was started on mechanical ventilation. PET scan whole body (Figure: 3) revealed thymic mass regression abutting the left main pulmonary artery, infiltrating the pericardium and an enlarged subcarinal lymph node suggestive of infiltrative thymoma.

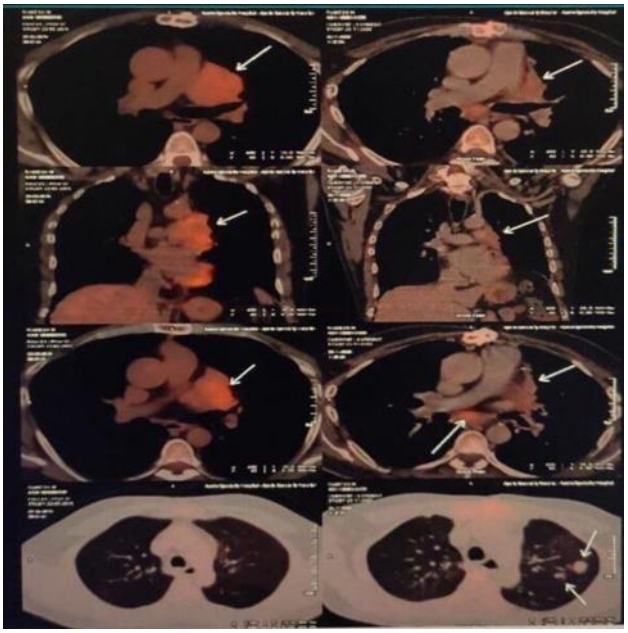

Figure 3: PET-CT whole body showing features suggestive of infiltrative thymoma.

Cardiothoracic surgeon opined that it is inoperable at this stage. In December 2020, was admitted again for fever (102°F), generalized weakness and shortness of breath. On examination, the patient was conscious, oriented, and febrile (Temp: 100.6°F) and tachypneic (RR: 30/min). His oxygen saturation on room air was initially normal, but he became hypoxic (86%) in 1-2 hours, and he required NIV support in Emergency Room. Labs showed anaemia and leucocytosis. He was started on IV antibiotics in suspicion of urosepsis and Ganciclovir was continued. Intravenous Immuno Globulin was given along with the escalation of the dose of pyridostigmine for the myasthenic crisis. He was intubated and mechanically ventilated.

He developed an inferior wall mi precipitating a complete heart block. A temporary pacemaker was emergently inserted via the central port. He underwent coronary angioplasty with intraaortic balloon catheter insertion in view of severe cardiogenic shock. Despite all resuscitative measures, he succumbed to illness on the fifth day of admission.

DISCUSSION

S.stercoralis infection was first detected in French soldiers on duty in Vietnam, in the year 1876 while the disseminated infection was first reported in 1966.[5,6] It can present with pulmonary, cutaneous or gastrointestinal symptoms like in our patient. Eosinophilia may be the only sign, but this is not reliable when patients are immunosuppressed.[7] The eosinophil count was not high in our patient, probably due to prolonged corticosteroid therapy.

Strongyloidiasis is particularly important in patients receiving immunosuppressive drugs such as corticosteroids and chemotherapy for cancer and hematologic malignancies. In the hyperinfection syndrome, the classic life cycle of S. stercoralis from the skin to lungs and gastrointestinal tract is accelerated with increased reproduction leading to excessive worm burden, whereas in disseminated strongyloidiasis, there is widespread dissemination of larvae outside the gut and lungs, often involving the liver, brain, heart, and urinary tract.[7] Glucocorticoids may accelerate rhabditiform larvae's transformation to invasive filariform larvae, which may trigger the auto-infective stage and lead to fatal hyperinfection.[8] Our patient was on steroid therapy for five years and MMF for two years in a background of poorly controlled type-2 diabetes mellitus, which puts him at high risk for hyperinfection. His retroviral status tested twice was negative.

Stool examination for the parasite is less sensitive, even after three stool examinations; positivity does not exceed 46%.[9] Endoscopic evaluation is the most sensitive diagnostic procedure for strongyloidiasis, as worms and their maturing larvae colonize in the duodenum. Our patient's routine examination of the stool was notable for eggs and larval forms of ancylostoma duodenale. Only endoscopic study helped in identifying co-existing strongyloidiasis. Thus, regular screening by serological testing or stool examination for parasitic infections such as strongyloidiasis should be carried in immunosuppressed patients, to prevent or delay the associated complications. We treated him with Ivermectin. Ivermectin is more effective in treating gastrointestinal strongyloidiasis and is considered the first-line therapy of Strongyloides hyperinfection.

He had severe gram-negative urosepsis (*Klebsiella Pneumoniae and Pseudomonas Aeruginosa*) and CMV enteritis with viremia on subsequent admission. Chronic MMF therapy in myasthenia gravis patients may trigger serious infections like CMV, EBV etc.[10] He had to be treated with a prolonged course of IV antibiotics, antivirals and the recovery from these superinfections was slow even with prompt management. Steroids were tapered off, and MMF was discontinued in view of recurrent sepsis, but then he presented with myasthenic crisis. It remains unclear whether infections trigger autoimmunity, which renders the individual more susceptible to further infectious agents. Holbro et al, in a large retrospective study, suggested that there should be a high index of suspicion for complex infections and autoimmune diseases in thymoma patients.[2] CMV infection is potentially fatal, and recurrent gram-negative sepsis made it challenging to manage in the setting of severe immunodeficiency status. Recurrent thymoma indicates poor prognosis and managing multiple infections effectively can prolong the survival rate and increase the quality of life.

CONCLUSION

There are no specific treatment strategies for the treatment of infections or autoimmunity in thymoma patient. Strongyloidiasis is treatable but can be a potentially life-threatening infection, especially in immunosuppressed patients. Clinicians should have a high index of suspicion of strongyloidiasis infection in patients on steroid therapy with gastrointestinal signs and symptoms. Eosinophil count may not be considered as an indicator if the patient is on immunosuppressants. Stool examination may not always be rewarding and endoscopic biopsy, and HPE may be needed to establish the diagnosis. Patients on long term MMF therapy are at increased risk of CMV infection. Viral serology testing and prophylactic antiviral agents should be considered, particularly in elderly Myasthenia patients.

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