PSEUDO-GAUCHER CELLS IN DISSEMINATED ATYPICAL MYCOBACTERIAL INFECTION - A CASE REPORT

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Abstract:
Atypical Mycobacteria also known variably as Mycobacteria other than tubercle (MOTT), Non Tuberculous Mycobacteria (NTM) and Environmental Mycobacteria (EM)(1) are ubiquitous in the environment existing in soil and water, as pathogens in birds and cattle and as pharyngeal flora in clinically well humans(2). Only rarely described as an invasive pathogen in immunocompetent humans, they frequently cause disseminated disease in patients with primary and acquired immunodeficiency syndrome. One such case is presented here. A 19 year old female presented with cervical lymphadenopathy, cough with expectoration, low grade intermittent fever, loss of weight, loss of appetite, abdominal pain, vomiting and diarrhea. On examination the patient was thin built, ill nourished and pale. She had generalized lymphadenopathy, organomegaly and opportunistic infections. She was treated in the past 5 times as a case of tuberculosis. She had normal plasma glucose and she tested negative for HIV ELISA. Histopathological examination of the lymph node received showed sheets of Pseudo-Gaucher cells. Sections stained by Ziehl-Neelsen showed acid fast bacilli loaded within the histiocytes (Pseudo-Gaucher cells).

Keyword:
Pseudo-Gaucher cell, Atypical mycobacteria, Mycobacterium avium intracellulare.

CASE REPORT:
19 year old unmarried female presented with cervical lymphadenopathy, cough with expectoration, low grade intermittent fever, loss of weight, loss of appetite, abdominal pain, vomiting and diarrhea. On examination the patient was thin built, ill nourished and pale. She had generalized lymphadenopathy, moderate hepatosplenomegaly, oral candidiasis and herpes labialis. She was given Anti Tuberculous Treatment (ATT) 5 times in the past since her 5yrs of age when she presented with similar episodes of cervical lymphadenopathy. The swelling regressed for a while and recurred in few months.
Computed Tomography (CT) of abdomen revealed multiple enlarged mesenteric, paraaortic, paracaval, external iliac and inguinal lymph nodes with omental cakes and thickened small bowel loops.

Cervical lymph node was biopsied and the same was received for Histopathological examination.

MACROSCOPY:
Two lymph nodes received larger one measuring 2cms in diameter. Cut surface – grey white, soft to firm in consistency. No necrosis seen. All of them embedded.

MICROSCOPY:
Sections stained with hematoxylin and eosin showed structure of lymph node replaced by sheets of large pale histiocytes with intervening residual scanty lymph node parenchyma (Fig1&2). The histiocytes have abundant pale foamy cytoplasm with small dark nucleus without pleomorphism or mitosis – morphology consistent with PSEUDO-GAUCHER CELL (Fig4). There is no evidence of giant cell, necrosis or granulomas (Fig3).

Fig 1: H&E 40x magnification – the lymph node architecture is effaced

Fig 2: H&E 100x magnification – lymph node structure with no follicles and depleted lymphocytes
Fig 3: H&E 100x magnification – lymph node structure replaced by sheets of large pale histiocytes. No granulomas, necrosis or giant cells.

Fig 4: H&E 400x magnification: cell populations replaced by sheets of large pale histiocytes with foamy cytoplasm with small dark nuclei – pseudo Gaucher cells.

SPECIAL STAIN:
In view of recurrent infections since many years and the presence of co existent opportunistic infections such as candidiasis and herpes, an infectious etiology was considered rather than a storage disorder despite the presence of large histiocytes resembling Gaucher cells. Hence sections were stained by Ziehl-Neelsen stain which showed large foamy histiocytes containing huge amounts of acid fast staining mycobacterium avium intracellulare (Fig5&6).

Fig 5: 100x - Ziehl Neelsen stain reveals large amounts of acid fast bacilli.
Fig 6: 1000x – Ziehl Neelsen stain showing foamy histiocytes containing huge amounts of acid fast staining mycobacterium avium intracellular

DIAGNOSIS:
Presence of Pseudo gaucher cells and well demonstrable acid fast bacilli points to a diagnosis of Atypical Mycobacterial Infection. In correlation with clinical history of recurrent infections since childhood, recurring lymphadenopathy, CT evidence of generalized lymphadenopathy, presence of opportunistic infections such as oral...
candidiasis and herpes, peripheral blood pancytopenia suggesting a possible bone marrow infiltration and recurrent diarrheal episodes with evidence of thickened small bowel loops in CT abdomen suggesting Gastrointestinal tract involvement, a final diagnosis of “DISSEMINATED ATYPICAL MYCOBACTERIAL INFECTION” was made. Since Diabetes mellitus and Acquired Immune Deficiency Syndrome (AIDS) were ruled out, the possibility of primary immunodeficiency was thought of.

**DISCUSSION:**
Atypical mycobacteria or Non Tuberculous Mycobacteria (NTM) are common in watery environments such as marshes and lakes. Human contact occurs by drinking water, inhalation of aerosols or by inoculation into skin wounds (2). Direct human to human transmission is not known to occur (3). They occur as transient commensals on the skin, pharynx, gastrointestinal tract, lower urethra and external genitalia (1). The atypical mycobacteria most frequently associated with human disease causing cervical lymphadenopathy and disseminated infection are as follows:

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<td><strong>DISEASE</strong></td>
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Atypical Mycobacterial lymphadenitis affects children aged 1-12 years (2). In most cases a single cervical or preauricular node is involved. If more than one node or other sites are affected, should arouse suspicion of immunodeficiency. Patients with disseminated disease due to atypical/ non tuberculous mycobacteria have predisposing conditions such as cancer, autoimmune disease, post transplant immunosuppressive therapy, high dose corticosteroid therapy, congenital immunodeficiency and HIV disease (5). The manifestations of disseminated infection includes generalized lymphadenopathy, anemia and leucopenia secondary to bone marrow infiltration and vomiting, abdominal pain, diarrhea due to infiltration of intestinal wall (6). Upper gastrointestinal studies may reveal dilatation and thickening of the mucosal folds of the small bowel which may be clinically indistinguishable from lymphoma. Multiple large retroperitoneal and mesenteric lymph nodes are often demonstrated on abdominal computed tomographic scans (7). Lymph nodes involved by Mycobacterium features includes partially or totally effaced architecture, inapparent follicles,
Avium Intracellularare (MAI) are indolent and moderately enlarged. The histopathological nodes usually lack granulomas, giant cells, necrosis, calcification and fibrosis. Staining with Ziehl–Neelsen reveals large amounts of acid-fast bacilli engulfed by the distended histiocytes. "Pseudo-Gaucher cells might be the morphological hall-mark of atypical mycobacterial infection in immunodeficiency."

The formation of Pseudo-Gaucher cell in non-tuberculous mycobacterial infection (NTM) has been attributed to macrophage activation defect. In general all the mycobacteria including atypical mycobacteria are intracellular microbes. Therefore, cell mediated immunity plays a dominant role in killing of these intracellular microbes. Among the T lymphocytes, CD4+ helper cells and its subset TH1 were recognized as key effector cells against Non Tuberculous Mycobacteria. The development of disseminated MAC disease was highly correlated with a low CD4+ T lymphocyte numbers. Mycobacteria are phagocytosed by macrophages and respond by producing IL-12. IL-12 activates TH1 lymphocytes and leads to secretion of IFN-γ, which activates macrophages to produce reactive oxidants leading to destruction of ingested microbes. IFN-γ also increase the expression of major histocompatibility complex and Fc receptors, and concentrate certain antibiotics intracellularly, thus explaining the absolute necessity of normal IFN-γ levels for effective antimicrobial treatment. Therefore, anti-MAI drugs are unable to eradicate Mycobacterium Avium Intracellularare (MAI) in the absence of immune recovery. The genetic basis of susceptibility to disseminated infection with Non Tuberculous Mycobacteria is accounted for by specific mutations in the IFN-γ/IL-12 synthesis and response pathways. Thus TH1 cells coordinate the activation of macrophages and constitute the most important cellular defense mechanism against intracellular mycobacteria. Pseudo-Gaucher cells are also seen in chronic myelogenous leukaemia, thalassaemia, multiple myeloma, acute lymphoblastic leukaemia, Hodgkin disease, non-Hodgkin lymphoma, and myelodysplastic syndrome. Here Pseudo-gaucher cell results from increased cell turnover and glucocerebroside deposition within macrophages. Therefore confirmation of atypical mycobacterial infection and species typing can be done in pathologic specimens using Polymerase Chain Reaction (PCR). The presence of MAI can be ascertained with PCR in paraffin sections also, but the sensitivity of the technique is not significantly greater than that of the acid-fast stains. MAC infection often requires multidrug therapy such as combination of macrolide (clarithromycin or azithromycin), ethambutol and a rifamycin.

CONCLUSION:
"Pseudo-Gaucher cells can be considered the morphological hallmark of mycobacterial infection in immunodeficiency. In the presence of Pseudo-Gaucher cells, AFB stains should be performed immediately and if positive, the patient should be evaluated for IFN-γ and IL-12 function which would help in deciding the curative drug regime (appropriate antimicrobials and IFN-γ). However, the presence of pseudo-Gaucher cells might predict a very poor outcome.

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