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Pathology

Cytophagic Histiocytic Panniculitis with Undetermined Autoimmune Disease: A Rare Case Report

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Abstract **Case Report**

Cytophagic histiocytic panniculitis is a rare disease, associated with either nonmalignant conditions or subcutaneous panniculitis-like T-cell lymphoma (SPTL), and often also associated with hemophagocytic lymphohistiocytosis (HLH). We report the case of a 63-year-old woman who developed a multiple tender, indurated, erythmatous lesions over the abdomen, back, trunk and limbs. Histopathologic findings from skin biopsy specimens revealed significant lobular panniculitis with benign histiocytes showing hemophagocytosis. ANA by IF was positive. Though it is very rare, to confirm diagnosis of CHP by histopathology is very important as CHP and SPLT may span a clinicopathologic spectrum in which there is a natural disease progression from CHP to fatal SPTL.

Keywords: Cytophagic histiocytic panniculitis (CHP), Hemophagocytic lymphohistiocytosis (HLH), Subcutaneous panniculitis-like T-cell lymphoma (SPTL).

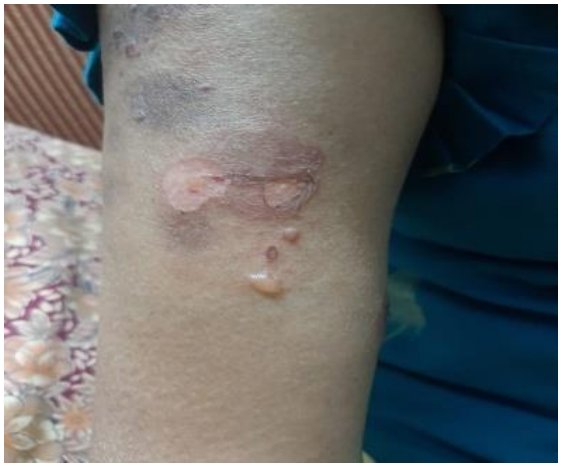
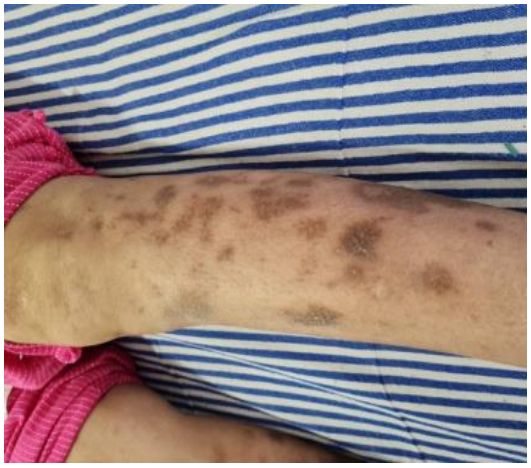
INTRODUCTION

Cytophagic histiocytic panniculitis (CHP) is a rare disease,first described in 1980, characterized by infiltration of subcutaneous adipose tissue by benign-appearing T lymphocytes and phagocytic histiocytes ("bean bag cells") [1]. CHP may be an isolated skin disease or associated with non-malignant conditions, such as infections, as well as malignancies, including subcutaneous panniculitis-like T-celllymphoma (SPTL), a rare form of non-Hodgkin lymphoma infiltrating into subcutaneous adipose tissue [2]. Subcutaneous panniculitis has been reported in a small number of patients with hemophagocytic lymphohistiocytosis (HLH), a life threatening condition characterized by uncontrolled activation and proliferation of T-cells resulting in hypercytokinemia, proliferation of histiocytes and hemophagocytosis [3, 4].

Patients with CHP may have three different clinical courses, mainly depending on isolated presentation or association with HLH. Some patients rapidly progress and often die within one year, due to sepsis, coagulation disorders and multi-organ failure. Some have recurrent bouts of reactivation and may survive for years. Some patients respond well to treatment and may have a normal life. We report a case of CHP in 64 year old female with multiple, painful, erythematous and indurated skin lesions on extremities, abdomen & back since 6 months successfully treated with azathioprine and steroids. Thus, it is important to diagnose CHP by histopathology to catagorize the course of disease as it can progress to fatal disorder.

CASE REPORT

A 63-year-old woman with a history of multiple, painful, erythematous and indurated skin lesions on extremities, abdomen & back since 6 months - waxing and waning. Few pigmented lesions noted. The result of general and systemic examination was within normal limits. Cutaneous examination revealed poorly defined multiple erythematous tender indurated subcutaneous lesions over the trunk and limbs.

Laboratory investigations:
CBC – Within Normal Limit
HIV, HbsAg HCV – Negative

Angiotensin converting enzyme (ACE) level was on the higher side- (96 U/L),

Autoantibody profile
Antinuclear Antibody: - +1
Anti Neutrophil Cytoplasmic Antibody - Negative

Other details:
Good response to Azathioprine and steroids.

CT scan - NO systemic involvement Punch biopsy was done previously before 6 month which was suggestive of erythema nodosum.

Histopathological Examination:
Gross Examination:
We received two specimen of skin biopsy taken from both arms

Right arm specimen (healed lesion): - 1.1x0.5 cm in size.
Left arm specimen (active lesion): - 2 fragments of skin tissue measuring 1.4x0.3 and 0.5x0.2 cm in size.

Histopathological Examination:

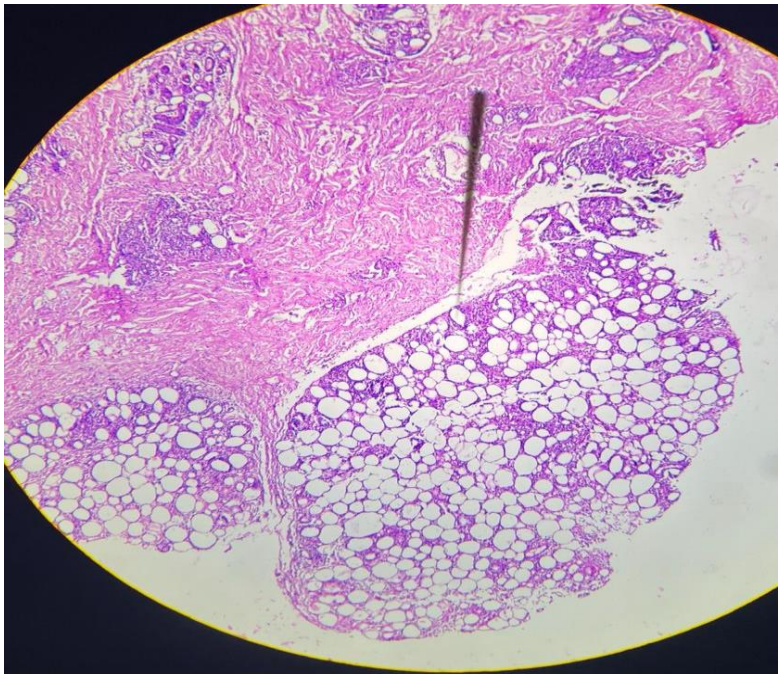


Figure 1: (1) Skin Biopsy from healed lesion (Right Arm) - Epidermis is atrophic. There is mild pericapillry infiltration with lymphocytes and occasional macrophage. The entire dermis shows fibrosis extending focally in subcutaneous tissue. Subcutaneous fat also shows perivascular lymphocytic & histiocytic infiltration

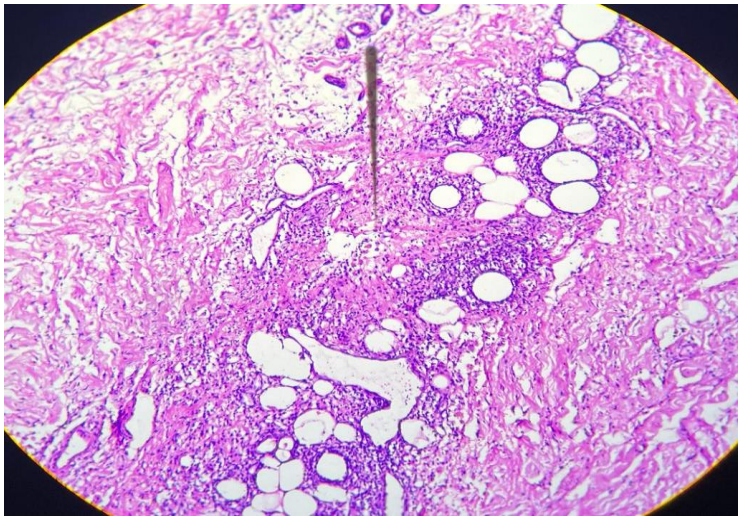


Figure 2: Skin Biopsy from active lesion (Left Arm): hyperkeratotic Corneal layer of epidermis along with attached atrophic epidermis and edematous papillary dermis with hemorrhagic material adherent to the undersurface. The edematous Dermis and subcutaneous fatty tissue shows pericapillary and periadnexal infiltration with lymphocytes and histiocytes showing phagocytosis of RBCs along with extravasated RBCs. The subcutaneous fatty tisue shows predominantly lobular panniculitis (Figure 1 & 2)

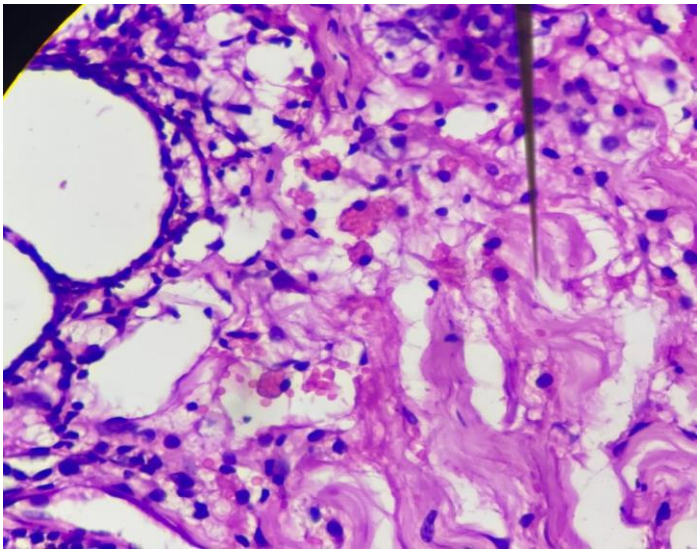


Figure 3: It shows infiltration of focally necrotic fatty tissue with lymphocytes, groups of histiocytes and few polymorphs. Many histiocytes in the adjoining loose septal and dermal tissue show phagocytosis of RBCs ('Bag of beans' appearance). Lymphocytic rimming or lymphoid follicle formation around fat cells not seen. Few histiocytes also show phagocytosis of nuclear debris. There is no evidence of vasculitis or epithelioid granuloma formation

DISCUSSION

1. The diagnosis of CHP relies mainly on the histopathology, which characteristically shows prominent chronic inflammation of the fat tissue infiltrated mainly by the benign appearing T lymphocytes and the occasional phagocytic histiocytes (bean bag cells) [5]. Erythrophagocytosis and cytophagocytosis by benign-appearing histiocytes can also be observed in internal organs, particularly the lymph nodes, spleen, liver, and bone marrow.[6]

Our case is worthy of description for several reasons. First, there is no mention in the literature of autoimmune involvement in patients with CHP.

Although the exact etiology of HPS (Hemophagocytosis Syndrome) is still not clear, numerous diseases have been shown to be associated with HPS, which include hematological diseases such as acute leukemia, malignant lymphoma, infections (viral, bacterial, fungal, and parasitic). Human immunodeficiency virus (HIV) infections are one of the infectious etiologies considered to be associated with HPS, and it is recommended that all suspected patients with HPS be screened for HIV. Systemic autoimmune

diseases, such as SLE and adult-onset Still's disease, have also been reported to be associated with HPS [6, 7, 8-10].

The clinical manifestations can be attributed to increased secretion of cytokines from activated T/NK cells and macrophages, which, in turn, suppress the hematopoiesis by causing prominent hemophagocytosis in the bone marrow, spleen, liver, and lymph nodes. While some patients with CHP suffer from relatively indolent variants of the disease, many others die as a result of massive visceral hemorrhage or organ system failure [6].

Once CHP is suspected, the diagnosis relies mainly on histopathology findings. In such context, discriminating between CHP and SPTL is therapeutically important because nonmalignant CHP often improves under pulses of high-dose intravenous methylprednisolone and cyclosporine A [11], whereas most cases of SPTL may be best treated withmore aggressive therapy. Marzano *et al*., [12] suggested that these conditions might span a clinical-pathological spectrum in which there is a natural progression from CHP to SPTL. Since the distinction of CHP from SPTL is difficult and CHP might be a precursor of SPTL [13], some authors proposed to use the term "panniculitis-like subcutaneous lymphoma with cytophagocytosis" instead of CHP, even when T-cell clonality was not documented [14]. This approach would have a beneficial effect on treatment planning towards oncological rather than anti-inflammatory therapy. Bader-Meunier *et al*., [15] recently emphasized that HLH-associated CHP may be diagnosed despite monoclonal T-cell proliferation that mimics SPTL and is best treated by prednisone and cyclosporine A, atleast in children. It has been suggested that this florid clonal T-cell proliferation is reactive, probably driven by astrong immune reaction against EBV infection [16]. Further more, Huppmann *et al*., [17] confirmed that molecular studies are diagnostically helpful but not specific, since the absence of clonality does not rule out the diagnosis of SPTL.

The diagnosis of CHP is challenging, but it was supported by several data in our case. Although many histopathological findings are common to both CHP and SPTL, rimming of the fat vacuoles by atypical lymphoid cells is a useful diagnostic feature for SPTL [18].

In our case, involvement of the trunk, back, extremities, good response to therapy, lack of relapse after treatment discontinuation, and absence of characteristic histopathology findings of lupus erythematosus supported the diagnosis of CHP.

Cytotoxic chemotherapy should be considered for relapsing/refractory disease or more severe forms [19]. High-dose chemotherapy followed by autologous peripheral blood stem cell transplantation may be necessary for the treatment of particularly aggressive CHP [20].

Patients with CHP may have three different clinical courses, mainly depending on isolated presentation or association with HLH. Some patients rapidly progress and often die within one year, due to sepsis, coagulation disorders and multi-organ failure. Others have recurrent bouts of reactivation and may survive for years. Other patients respond well to treatment and may have a normal life.

Gonzales *et al*., frist described T-cell lymphoma involving subcutaneous tissue as a rare, distinct subset of peripheral T cell lymphoma (PTL) characterised by propensity to be associated with a hemophagocytic syndrome and by an aggressive clinical course. This entity was characterized as a subtype of PTL by International Lymphoma Study Group in1994 under the term subcutaneous panniculitis –like T-cell lymphoma (SPTL). Thus, both the precise nature of SPTL and overall complex relation between CHP and SPTL remain to be clarified.

Peters and Winkelmann suggested that CHP might be a preneoplastic syndrome or a reactive process to a neoplastic disease. In fact, it is well known that erythrophagocytic syndromes occur uncommonly in a multitude of disorders, including infectious and neoplastic conditions.

According to Wang *et al*., CHP is probably a low grade T-cell lymphoma that with time might progress to more aggressive SPTL.

CONCLUSION

CHP is a rare and often fatal form of panniculitis with multisystem involvement. However, it can also present in a benign form involving only the subcutaneous tissue, thus having a broad clinical spectrum.

Our observation suggest that it does not seem appropriate to differentiate SPTL and CHP and that, on contrary, there is a natural disease progression from CHP to SPTL.

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