

Avoid a rash diagnosis: Cytophagic histiocytic panniculitis is a distinct clinical entity

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Case Report

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Abstract

Background: Cytophagic histiocytic panniculitis (CHP) is a rare autoimmune disease that can mimic both lupus panniculitis (LP) and subcutaneous panniculitis-like T cell lymphoma (SPTL). Diagnosis is challenging due to overlapping histologic characteristics of these entities. It has historically been considered a pre-malignant lesion, with few case reports detailing CHP as its own entity.

Case Presentation: We describe two cases of panniculitis with histologic features similar to both LP and SPTL. Neither patient had clinical or laboratory features convincing of systemic lupus erythematosus (SLE), which made a diagnosis of LP unlikely; T-cell receptor (TCR) gene rearrangement studies demonstrated a polyclonal lymphocytic infiltrate, suggestive of a non-malignant process. Both patients were diagnosed with CHP and responded well to tacrolimus therapy.

Conclusions: CHP is a distinct clinical entity, and the panniculitis need not fall under a diagnosis of LP or SPTL. TCR gene rearrangement studies are an essential part of the evaluation to demonstrate polyclonality of the benign lymphocytic infiltrate. T-cell directed therapy represents a rational approach to treatment and yielded success in these two patients.

Background

Cytophagic histiocytic panniculitis (CHP) is a poorly understood inflammatory disorder of the subcutaneous adipose tissue. A 1981 series of five patients were reported to have panniculitis associated with episodes of fever, progressive liver dysfunction, and severe hemorrhagic diathesis. Skin biopsies revealed lobular panniculitis with fat necrosis, specifically with infiltration of subcutaneous adipose tissue by benign-appearing T-lymphocytes and phagocytic histiocytes that rimmed the adipocytes (1–3). This constellation of findings was termed cytophagic histiocytic panniculitis due to the characteristic histiocytic “bean bag cells” demonstrating phagocytosed cellular elements (1, 2). These cells appear benign with normal-appearing nuclei and a normal nucleus to cytoplasm ratio (1–3).

CHP may manifest as isolated cutaneous nodules, but it is more commonly accompanied by systemic features that range in severity, the most morbid of which is hemophagocytic lymphohistiocytosis (HLH). This phenotype is associated with uncontrolled macrophage and CD8 + T-cell activation which stimulates production of inflammatory cytokines, particularly interferon-gamma (IFN- γ). This results in exuberant systemic inflammation, fever, hepatosplenomegaly, liver failure, disseminated intravascular coagulation, and pancytopenia (4–6).

CHP should be considered as part of the differential diagnosis in children and adults with panniculitis, or nodular inflammation of the subcutaneous fat. Its two biggest mimickers include lupus panniculitis (LP) and subcutaneous panniculitis-like T cell lymphoma (SPTL), and while the three entities can look grossly and histologically similar, treatment may differ drastically.

LP represents only 1–3% of patients with cutaneous lupus erythematosus and can occur in isolation or, more commonly, as part of systemic lupus erythematosus (SLE). The subcutaneous infiltrate surrounds the adipocytes in a distribution similar to CHP and SPTL. However, the cell types are mostly lymphocytes and plasma cells, with few histiocytes, in contrast to the greater histiocytic presence of CHP (3, 4, 8). The cells of LP typically do not exhibit morphologic atypia, and the $\alpha\beta$ or $\gamma\delta$ T-cell receptors (TCR) are polyclonal, features that are distinct from malignancy (3, 4). In contrast, the lymphocytic infiltrate of SPTL, a rare lymphoma of the subcutaneous adipose tissue, demonstrates atypical CD3+/CD4- T-cells with hyperchromatic, pleomorphic nuclei and irregular nucleolar membranes, admixed with macrophages (4, 5). Cytokines secreted by these monoclonal T-cells prompt hemophagocytosis by proximate histiocytes (6) and may result in fulminant HLH and rapid clinical decline (6–9).

CHP and SPTL were previously thought to be benign and malignant extremes of the panniculitis spectrum, respectively, with CHP considered a pre-cancerous lesion (10, 11). However, several cases have since been reported in the literature describing CHP as an isolated entity, without ever undergoing malignant transformation (10, 12). The diagnostic difficulty lies not only in the histologic similarity between CHP, SPTL, and LP, but also in the awareness that each can be associated with systemic symptoms which, in some cases, progress to the hemophagocytic syndrome. Here we present two such cases of panniculitis of unclear etiology that were ultimately diagnosed as CHP, further supporting the notion that this exists as a unique pathologic process.

Case Presentation

Case 1

An 11-year-old girl with sickle cell trait and alpha thalassemia trait presented with dry, indurated, warm, erythematous patches on the left buttock and upper thigh that had been present for one month, and she was treated with oral antibiotics for presumed cellulitis. During the cephalexin course the skin became painful, and she developed daily, high fevers. Physical exam was notable for a well-appearing child with the affected areas weeping serosanguinous fluid. Laboratory data were significant for leukopenia with lymphopenia and neutropenia, anemia with reticulocytopenia, mildly elevated aspartate aminotransferase (AST), and elevated lactate dehydrogenase (LDH); inflammatory markers, uric acid, and peripheral blood smear were normal, the latter showing no evidence of blast cells or hemolysis (Table 1). While HLH was considered due to the continuous fever and cytopenias, there was no hepatosplenomegaly or other consistent laboratory abnormalities including hyperferritinemia, hypofibrinogenemia, or hypertriglyceridemia. Ultrasound of the lesion showed increased echogenicity of the subcutaneous fat, and magnetic resonance imaging (MRI) similarly showed findings suggestive of extensive soft tissue cellulitis with possible early myositis. Skin biopsy demonstrated a dense inflammatory infiltrate within the dermis and dermal-epidermal junction, consisting primarily of lymphocytes, macrophages, and plasma cells, without granulomas; the deep subcutaneous fat was not sampled. Wound culture was positive for *Enterobacter cloacae* and Methicillin Resistant *Staphylococcus aureus*, and after 1.5 weeks of ciprofloxacin treatment, her fever subsided. Due to the absence of

expected systemic inflammation in the setting of infection, an extensive immunodeficiency evaluation was performed but was largely unrevealing for innate, humoral, and cellular defects. Though the patient remained afebrile for the next two months, her skin abnormalities persisted.

Over the following eight weeks, new non-tender, indurated nodules erupted on her arms and legs, followed by recurrence of fever and newly elevated inflammatory markers; erythrocyte sedimentation rate peaked at 57 mm/hr, though C-reactive protein remained normal. Additional laboratory data at this stage were significant for a low titer positive antinuclear antibody (ANA) 1:80 without specific antibodies to extractable nuclear antigens. Positron emission tomography with MR sequences showed non-specific abnormal fluorodeoxyglucose uptake at the areas of subcutaneous involvement and at scattered lymph nodes, but neither were concerning for neoplastic metabolic activity. Biopsy of a nodule showed histologic and immunohistochemical features of extensive lymphohistiocytic panniculitis. Among the infiltrate of mature CD4 + and CD8 + T-lymphocytes and CD163 + histiocytes surrounding fat lobules were atypical lymphocytes bearing larger, irregular nuclei, initially prompting concern for lymphoma (Fig. 1, 2). Also noted were more T-cells expressing TCR- γ than TCR- β . However, TCR- γ and TCR- β gene rearrangement studies did not demonstrate monoclonality, thereby essentially excluding SPTL and $\gamma\delta$ -T-cell lymphoma, despite the atypical cellular appearance. Additionally, the low-titer ANA without other clinical features of SLE dramatically lowered suspicion for LP. CHP was considered the most rational diagnosis, so steroids and T-cell targeted therapy with tacrolimus, a calcineurin inhibitor, were initiated and titrated to a goal level of 5–10 mg/mL. The patient initially demonstrated a good response as the lesions decreased in size, the cytopenias improved, and she remained afebrile. In association with a discontinuation of therapy, the panniculitis lesions recurred, though without a robust rebound of the fever, cytopenias, or systemic inflammation.

Table 1
Laboratory data of Patient 1 and Patient 2.

Laboratory Test	Patient 1	Patient 2
WBC	2.3 K/ μ L (4.3–11.4)	2.3 K/ μ L (3.8–10.6)
ALC	0.9 K/ μ L (1.2–4.3)	0.12 K/ μ L (1.1–4.0)
ANC	1.1 K/ μ L (1.6–7.9)	2.0 K/ μ L (1.8–7.7)
Hemoglobin	10 g/dL (11.5–15.5)	8.8 g/dL (12.0–15.0)
Platelets	226 K/ μ L (150.0–400.0)	121 K/ μ L (150.0–450.0)
ESR	16 mm/hr (0–20.0)	Not available
CRP	< 0.5 mg/dL (0–0.9)	Not available
AST	70 U/L (10–40.0)	313 U/L (0–35.0)
ALT	20 U/L (10–35.0)	415 U/L (0–52.0)
Direct Bilirubin	0.2 mg/dL (0–0.3)	2.6 mg/dL (0–0.3)
Ferritin	144 ng/mL (10.0–82.0)	23,165 ng/mL (11–307.0)
Fibrinogen	257 mg/dL (172.0–471.0)	62 mg/dL (200–450.0)
PT	Not available	16.9 sec (12.1–14.5)
PTT	Not available	32 sec (22.0–36.0)
Triglycerides	70 mg/dL (28.0–129.0)	472 mg/dL (40.0–200.0)
LDH	1,231 U/L (380.0–770.0)	1,530 U/L (0–250.0)
Uric acid	3.5 mg/dL (3.0–4.7)	4.2 mg/dL (1.5–6.5)

WBC, white blood cell count; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine transaminase; PT, prothrombin time; PTT, partial thromboplastin time; LDH, lactate dehydrogenase

Case 2

A 26-year-old previously healthy female presented with persistent fever. The frequency was initially once to twice per week, but then progressed to daily and was unresponsive to antipyretics. During this period, she developed an erythematous, painful nodule on her right thigh with an adjacent large inguinal lymph node. The lesion was thought to be cellulitis, but it persisted along with the fever, despite antibiotics. She underwent multiple admissions for presumed sepsis, but a variety of broad-spectrum antibiotics had no effect on her fever. Inguinal lymph node excisional biopsy showed benign-appearing lymphoid tissue with adjacent lymphocytic lobar panniculitis, which in conjunction with a positive ANA 1:640 and a history of Raynaud's phenomenon, prompted a tentative diagnosis of SLE. Treatment with steroids, hydroxychloroquine, and mycophenolate mofetil (MMF) yielded a brief hiatus in fever, but it recurred as

the steroids were tapered. By this time, she developed new abdominal pain with associated jaundice, hepatosplenomegaly, and ascites. Laboratory data were significant for pancytopenia, decreased fibrinogen, and elevated transaminases, direct bilirubin, LDH, ferritin, and triglycerides (Table 1). Bone marrow biopsy was planned for evaluation of hemophagocytosis or an infiltrative process but was deferred due to logistical considerations. A diagnosis of secondary HLH was established on the basis of fever, splenomegaly, pancytopenia, hepatic dysfunction with intravascular coagulation, and hyperferritinemia. She received three doses of etoposide and dexamethasone, with improvement of fevers, cytopenias, and liver injury, though mild abdominal pain and distension persisted. Due to the uncertain nature of her underlying illness, the patient was referred to our institution for evaluation. History and physical exam were not indicative of any clinical manifestations of SLE, and repeat serologic testing yielded a low-titer ANA 1:160 without specific antibodies to extractable nuclear antigens, bringing into question whether SLE was the principal trigger of the HLH. Upon review, the nodal and adjacent tissue biopsies were consistent with a reactive lymph node and lymphocytic lobular panniculitis, respectively. The adipose tissue displayed an extensive lymphocytic infiltrate with CD163 + activated histiocytes rimming the adipocytes. The lymphocytes were mostly T-cells with very few B-cells. Many of the CD8 + T-cells exhibited morphologic atypia with irregular nuclei; most expressed TCR- β and few expressed TCR- γ . Flow cytometry was not concerning for immunophenotypic B- or T-cell aberrancies, and TCR gene rearrangement studies were not indicative of a monoclonal cellular proliferation. A diagnosis of lymphoma was considered unlikely, despite the atypical morphology of the T-cells. Though the possibility of LP had previously been considered, the paucity of B-cells argued against this diagnosis. Furthermore, isolated LP in the absence of SLE would not have been expected to induce HLH physiology. As LP and SPTL were reasonably excluded, underlying pathology and etiology of the HLH episode were ascribed to CHP. Hydroxychloroquine and MMF were discontinued, tacrolimus was started and titrated to a goal level of 5–10 mg/mL, and oral steroids were tapered. The patient had an excellent course and soon thereafter transitioned to adult care.

Discussion

As these two cases demonstrate, arriving at a diagnosis of CHP is challenging due to the broad spectrum of presentations. The systemic features accompanying the cutaneous nodules range from fever to a fulminant HLH syndrome, as seen in patients 1 and 2, respectively. CHP can mimic other causes of panniculitis with substantial histopathologic overlap with LP and SPTL. Tissue immunohistochemistry and TCR gene rearrangement studies, in combination with clinical context, ultimately led to diagnosis and successful treatment of our patients. We propose that in cases of suspected panniculitis in which the underlying etiology is ambiguous, biopsy with immunophenotypic and genetic profiling can direct diagnosis.

Specifically, assessment of lymphocytic clonality status should be used as a major tool to distinguish SPTL from CHP and LP; monoclonal TCR gene rearrangement is suggestive of malignant SPTL, whereas benign polyclonal gene rearrangement represents the majority of CHP and LP (3, 4). In both patients, TCR polyclonality strongly mitigated the likelihood of SPTL.

After SPTL is excluded, CHP and LP can be distinguished by a combination of clinical, laboratory, and histologic features. While CHP can manifest with painful nodules alone, it can be associated with systemic symptoms, in which case the course tends to be severe and often progresses to HLH (1). In contrast, if LP is associated with systemic features, the course is usually not as severe and rarely progresses to HLH, as demonstrated in a case series of seven patients with LP, in whom there were no mortalities over a median 64-month follow up period (13). Additionally, CHP can develop at sites of local trauma, so a history of recent trauma may invoke CHP more strongly than LP (3). From a serologic standpoint, CHP can be associated with ANA positivity, as seen in the majority of LP cases, and as was true in our patients (14). However, the absence of specific antibodies to extractable nuclear antigens is highly unusual for LP and substantiates a diagnosis of CHP. Histologic differences also aid in distinguishing these entities. CHP demonstrates a histiocytic predominance, with T-cells as the major lymphocyte subtype, whereas the infiltrate of LP has fewer histiocytes and a high plasma cell presence (1, 15, 16) (Table 2).

Table 2
Comparison of typical features of CHP, LP, and SPTL

Features	CHP	LP	SPTL
Clinical Manifestations	- Isolated cutaneous nodules - Systemic features	- Isolated cutaneous nodules - Usually part of SLE	- Isolated cutaneous nodules - Systemic features
Histologic Appearance	- Lymphocytes rim adipocytes - "Bean bag" histiocytes	- Lymphocytes rim adipocytes	- Lymphocytes rim adipocytes
Cellular Types	- Majority are histiocytes - Some lymphocytes	- Majority are lymphocytes and plasma cells - Few histiocytes	- Mixture of lymphocytes and macrophages
Cellular Morphology	- Often normal, but may exhibit atypia	- Normal	- Atypical
TCR Clonality	- Polyclonal	- Polyclonal	- Monoclonal

CHP, cytophagic histiocytic panniculitis; LP, lupus panniculitis; SPTL, subcutaneous panniculitis-like T cell lymphoma; SLE, systemic lupus erythematosus; TCR, T-cell receptor

Initial treatment of CHP consists of a combination of broad and targeted immunosuppression. Steroids serve to quickly quell systemic inflammation, with regimens based on severity of illness, but must be accompanied by a targeted steroid-sparing agent. Judicious steroid use is especially important when the

diagnosis is still unclear and SPTL is not yet entirely excluded. To address the T-cell mediated pathophysiology of CHP, the mainstay of therapy is the class of calcineurin inhibitors, which block Nuclear Factor of Activated T-cells signaling (17). Through this mechanism, tacrolimus and cyclosporine-A prevent T-cell activation and cytokine secretion, with the former demonstrating efficacy in our patients. In refractory disease, interleukin-1 (IL-1) blockade may be an alternative therapeutic approach; IL-1 receptor antagonist, anakinra, was used successfully in a patient with HLH secondary to CHP unresponsive to steroids, cyclosporine, and etoposide (12).

Conclusions

CHP is a distinct clinical entity that bears an array of presentations and can be histopathologically indistinguishable from SPTL and LP. In our two patients, a diagnosis of CHP was supported by a combination of immunophenotyping and TCR gene rearrangement studies showing TCR polyclonality, thereby essentially excluding a lymphomatous process. We propose that this mode of immunogenetic profiling be performed on panniculitis tissue samples when the underlying disease is equivocal, as assessment of clonality status in combination with clinical context is essential for diagnosis and appropriate treatment.

Abbreviations

CHP: cytophagic histiocytic panniculitis

LP: lupus panniculitis

SPTL: subcutaneous panniculitis-like T cell lymphoma

SLE: systemic lupus erythematosus

TCR: T-cell receptor

HLH: hemophagocytic lymphohistiocytosis

IFN- γ : interferon-gamma

AST: aspartate aminotransferase

LDH: lactate dehydrogenase

MRI: magnetic resonance imaging

ANA: antinuclear antibody

MMF: mycophenolate mofetil

IL-1: interleukin-1

Declarations

Ethics approval and consent to participate

This study was reviewed by The Committees for the Protection of Human Subjects (Institutional Review Board) at The Children's Hospital of Philadelphia and did not meet criteria for human subjects research, therefore the need for ongoing Institutional Review Board was waived.

Consent for publication

Written consent was obtained from the patients and/or their parents for all aspects of this publication.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JP drafted the initial manuscript. EJL revised the manuscript. EMB and MAL provided medical care to the patients and contributed intellectual material to the manuscript. MEP provided the figures. All authors approved the final manuscript as submitted.

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Figures

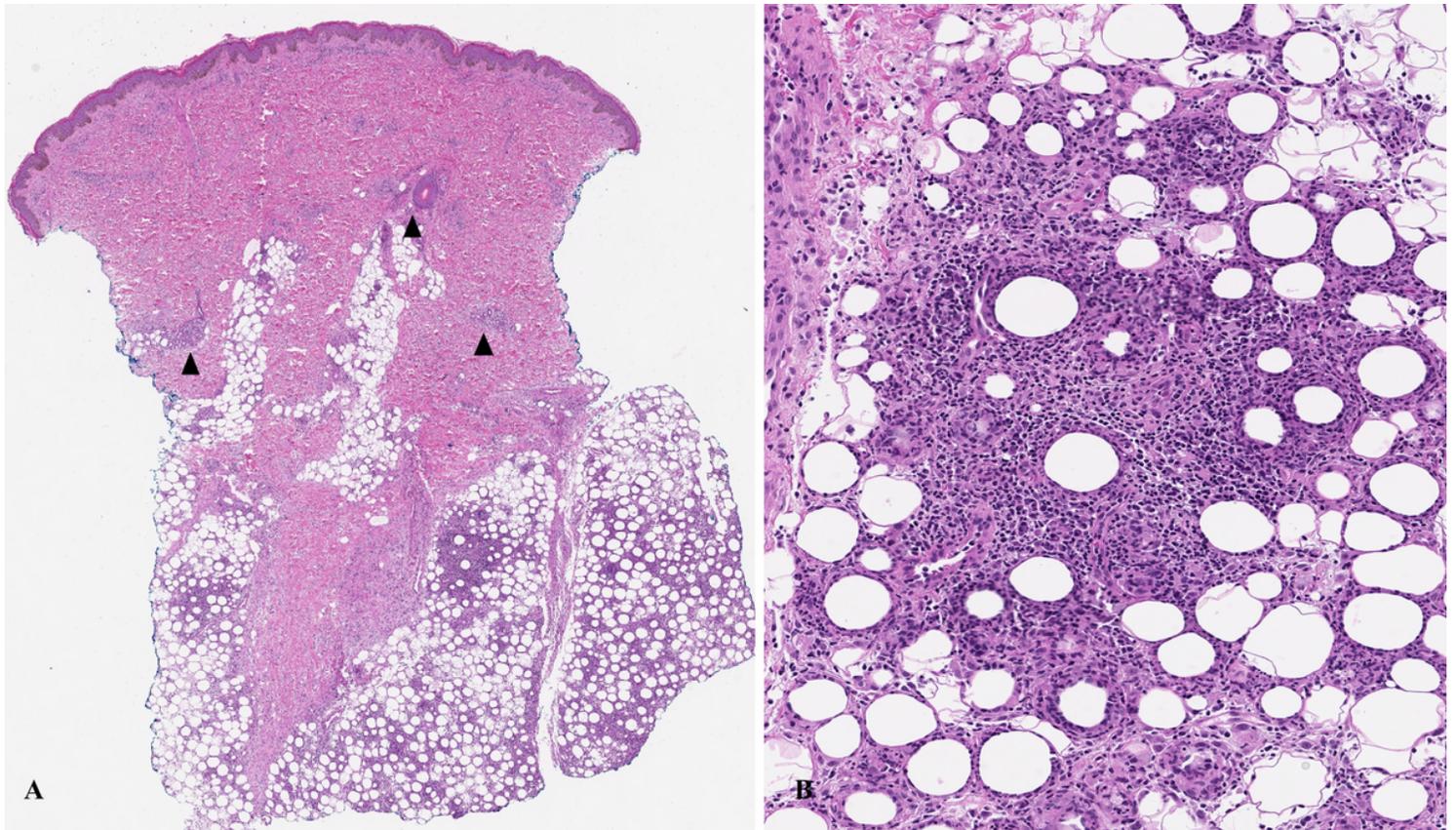


Figure 1

Punch biopsy of skin and subcutaneous tissue from Patient 1 stained with hematoxylin and eosin. A. There is perivascular and periadnexal inflammation in the dermis (arrowheads) and an extensive lymphocytic infiltrate in the subcutaneous tissue (x2 magnification). B. The infiltrate is composed of mature lymphocytes, occasional atypical lymphocytes, and histiocytes, which surround the fat cells (x20 magnification).

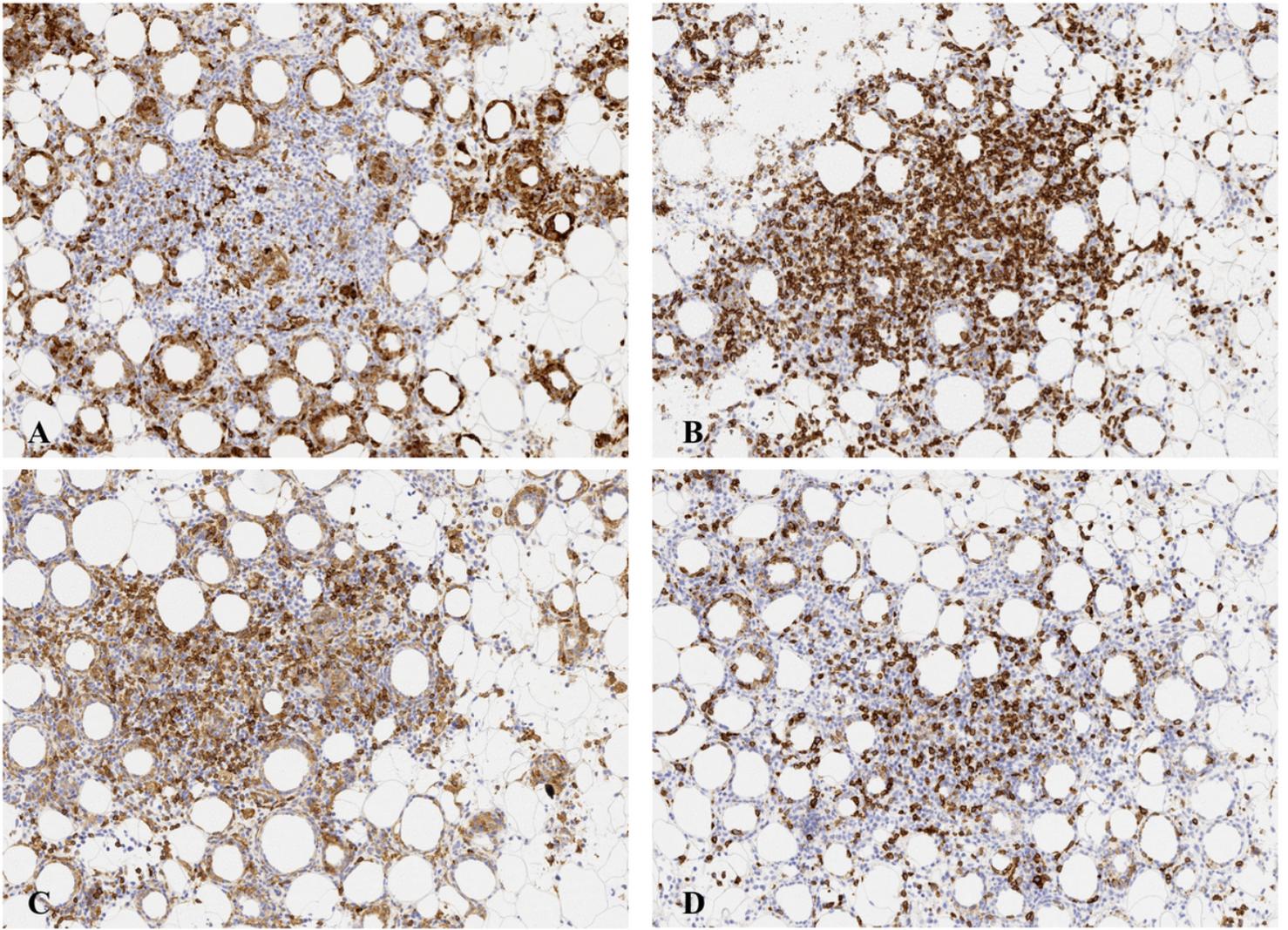


Figure 2

Immunohistochemical stains highlight the rimming of fat cells by T-cells and histiocytes from punch biopsy of Patient 1. A. Numerous CD163+ histiocytes and infiltrate surrounding adipocytes. B. The majority of lymphocytes are positive for CD3 and composed of an admixture of CD4+ and CD8+ T-cells. C. CD4 stain highlights a subset of T-cells and histiocytes. D. CD8 stain highlights a subset of T-cells (x20 magnification).