Avoid a rash diagnosis: reconsidering cytophagic histiocytic panniculitis as a distinct clinical-pathologic entity

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INTRODUCTION

Cytophagic histiocytic panniculitis (CHP) is a poorly understood inflammatory disorder involving the infiltration of subcutaneous adipose tissue by T-lymphocytes and phagocytic histiocytes rimming adipocytes.[1,2] These typically benign-appearing histiocytes demonstrate phagocytosed cellular elements, giving them a characteristic "bean-bag cell" appearance.[1] CHP's biggest mimickers include lupus panniculitis (LP) and subcutaneous panniculitis-like T-cell lymphoma (SPTL). Some consider CHP and SPTL benign and malignant extremes of the lymphohistiocytic panniculitis spectrum, respectively[3]; although classification criteria for CHP do not exist as they do for SPTL,[4] others consider CHP a distinct entity based on longstanding disease without malignant transformation.[2] We present 2 cases of panniculitis of initially unclear etiology, eventually diagnosed as CHP, while proposing a diagnostic approach to distinguish CHP from LP and SPTL. 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 the criteria for human subjects research; therefore, the need for an ongoing institutional review board was waived. Written consent was obtained from the patients and/or their parents for all aspects of this publication.

Abbreviations used:

ANA:	antinuclear antibody
AST:	aspartate aminotransferase
CHP:	cytophagic histiocytic panniculitis
HLH:	hemophagocytic lymphohistiocytosis
LDH:	lactate dehydrogenase
LP:	lupus panniculitis
MMF:	mycophenolate mofetil
SLE:	systemic lupus erythematosus
SPTL:	subcutaneous panniculitis-like T-cell lymphoma
TCR:	T-cell receptor
WBC:	white blood cell

CASE REPORTS

Patient 1

An 11-year-old girl presented with one month of daily fever and indurated, painful, erythematous plaques on the buttock and thigh. She had subcentimeter cervical and axillary lymphadenopathy without hepatosplenomegaly. Laboratory data revealed leukopenia (white blood cell count [WBC] of 2.3 K/μL, absolute neutrophil count of 1.1 K/μL, absolute lymphocyte count of 0.9 K/μL), anemia (hemoglobin 10 g/dL), elevated aspartate aminotransferase (AST; 70 U/L), and elevated lactate dehydrogenase (LDH; 1,231 U/L); complements, inflammatory markers, uric acid, and peripheral blood smear were normal (Table I). Wound culture grew methicillin-resistant *Staphylococcus aureus* and *Enterobacter*; fever resolved with antibiotics. However, over the following weeks, additional nodules erupted, with recurrence of fever, newly elevated inflammatory markers, low-titer antinuclear antibody (ANA) (1:80) without specific antibodies to extractable nuclear antigens, and negative serologic bacterial and viral studies. She was

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Table I. Laboratory data of patient 1 and patient 2

Laboratory test	Patient 1	Patient 2
WBC	2.3 K/μL (4.3-11.4)	2.3 K/μL (3.8-10.6)
ALC	0.9 K/μL (1.2-4.3)	0.12 K/μL (1.1-4.0)
ANC	1.1 K/μL (1.6-7.9)	2.0 K/μL (1.8-7.7)
Hemoglobin	10 g/dL (11.5-15.5)	8.8 g/dL (12.0-15.0)
Platelets	226 K/μL (150.0-400.0)	121 K/μL (150.0-450.0)
ESR	16 mm/h (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 s (12.1-14.5)
PTT	Not available	32 s (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)

Laboratory reference ranges are noted in parentheses.
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.

well-appearing with otherwise unremarkable examinatinon. Positron emission tomography showed abnormal uptake at the nodules without other evidence of neoplastic metabolic activity. Skin biopsy revealed lymphohistiocytic panniculitis, with CD4+ and CD8+ T-lymphocytes and CD163+ histiocytes surrounding the fat lobules. The lymphocytes appeared atypical, with large, irregular nuclei, concerning for lymphoma (Figs 1 and 2). However, there was a paucity of T-cell receptor (TCR)-beta-expressing cells, and gene rearrangement studies of TCR types γ and β did not demonstrate monoclonality, mitigating the possibility of SPTL and $\gamma\delta$-T-cell lymphoma. Fungal, bacterial, and acid-fast histochemical stains were negative. A paucity of lesional B cells lowered the suspicion for LP, and she did not meet classification criteria for systemic lupus erythematosus (SLE). Therefore, as isolated LP in addition to a non-SLE systemic illness was unlikely, combined with evidence against SPTL, a unifying diagnosis of CHP was made. CHP accounted for her cutaneous and systemic features, which responded to steroids and T-cell-directed therapy with tacrolimus. Over the next several years, she was nonadherent to medication and continued to develop nodules. The lack of new clinical manifestations was reassuring against LP or SPTL though repeat biopsy was not performed for histologic confirmation.

Patient 2

A 26-year-old woman presented with daily fever and an erythematous, painful thigh nodule. Biopsy showed lymphocytic lobular panniculitis, which, combined with a moderately high-titer ANA (1:640) and possible Raynaud's, prompted a tentative diagnosis of SLE. Fever remitted with steroids, hydroxychloroquine, and mycophenolate mofetil (MMF), but recurred with steroid tapering, and she developed new abdominal pain, hepatosplenomegaly, and subcentimeter cervical lymphadenopathy. Laboratory data demonstrated pancytopenia (WBC 2.3 K/μL, hemoglobin 8.8 g/dL, platelets 121 K/μL), hypofibrinogenemia (62 mg/dL), and elevated transaminases (AST 313, alanine transaminase 415), LDH (1,530 U/L), ferritin (23,165 ng/mL), and triglycerides (472 mg/dL) (Table I), consistent with secondary hemophagocytic lymphohistiocytosis (HLH). Fever, cytopenias, and transaminitis improved with etoposide and dexamethasone, and she was referred to our institution. She lacked clinical manifestations of SLE, and repeat testing yielded a low-titer ANA (1:160) without specific autoantibodies, questioning a diagnosis of SLE as the cause of HLH. Extensive infectious testing was negative, including serum bacterial, viral, and fungal testing; urine bacterial and fungal cultures; stool bacterial cultures; and acid-fast and fungal testing of the previously sampled tissue. Further tissue review showed an extensive, T-cell–predominant lymphocytic infiltrate with CD163+ activated histiocytes rimming adipocytes; the numerous histiocytes precluded assessment of the CD4/CD8 ratio. Many of the CD8+ T-cells exhibited morphologic atypia with irregular nuclei, suggestive of malignancy. However, flow cytometry did not show immunophenotypic

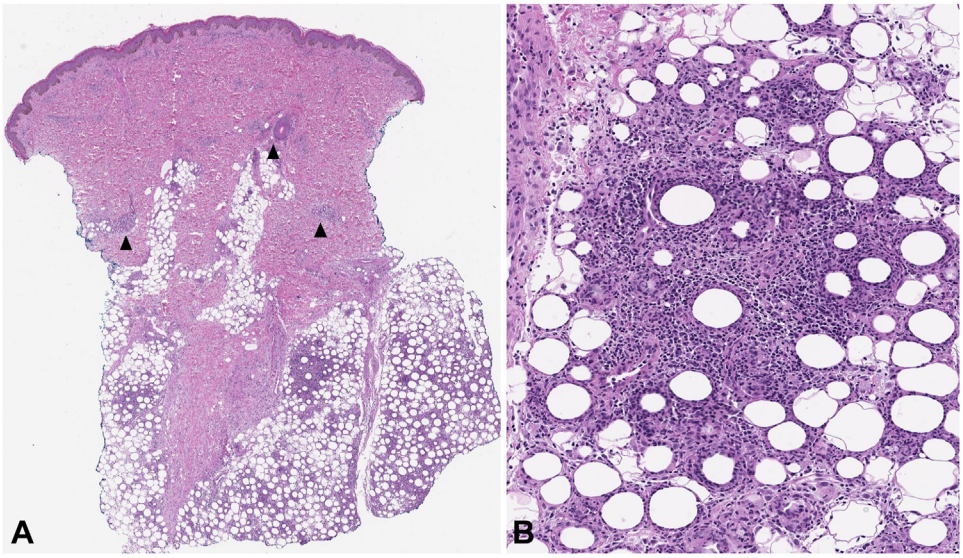

Fig 1. Punch biopsy of skin and subcutaneous tissue from patient 1 stained with hematoxylin and eosin. **A,** There is perivascular and periadnexal inflammation in the dermis (arrowheads) and an extensive lymphocytic infiltrate in the subcutaneous tissue (×2 magnification). **B,** The infiltrate is composed of mature lymphocytes, occasional atypical lymphocytes, and histiocytes, which surround the fat cells (×20 magnification).

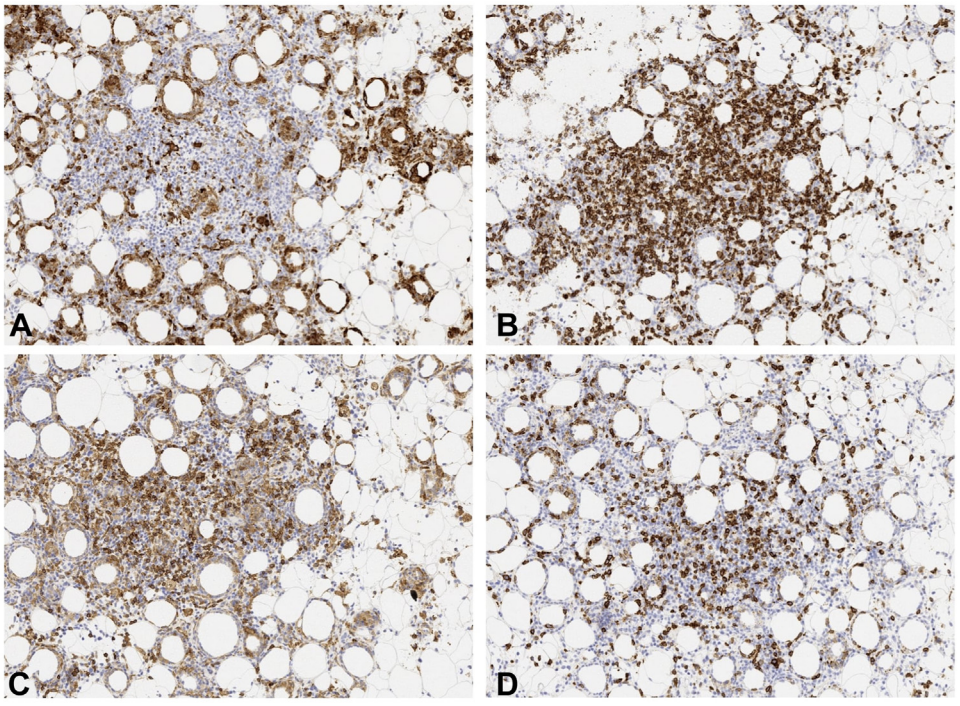

Fig 2. Immunohistochemical stains highlight the rimming of fat cells by T-cells and histiocytes from punch biopsy of patient 1. **A,** Numerous CD163+ histiocytes and infiltrate surrounding adipocytes. **B,** The majority of lymphocytes are positive for CD3 and composed of an admixture of CD4+ and CD8+ T-cells. **C,** CD4 stain highlights a subset of T-cells and histiocytes. **D,** CD8 stain highlights a subset of T-cells (×20 magnification).

aberrancies, and TCR gene rearrangement demonstrated polyclonality, making SPTL or other lymphoma unlikely; bone marrow biopsy was deferred. Isolated LP would unlikely induce HLH physiology without SLE; therefore, CHP was the most reasonable diagnosis. Hydroxychloroquine and MMF were

Table II. Comparison of typical features of CHP, LP, and SPTL

	CHP	LP	SPTL
Cutaneous manifestations	– Cutaneous nodules, with or without systemic features	– Cutaneous nodules, with or without systemic features	– Cutaneous nodules, with or without systemic features
Systemic manifestations	– Present in about half of the cases: – Constitutional symptoms – Cytopenias – Lymphadenopathy – Hepatosplenomegaly – Can progress to HLH	– Minorities can have concurrent SLE – Rarely progressed to HLH in the absence of SLE	– Present in about half of the cases: – Constitutional symptoms – Cytopenias – Lymphadenopathy – Hepatosplenomegaly – Can progress to HLH
Histologic appearance	– Lymphocytes rim adipocytes – "Bean-bag" histiocytes	– Lymphocytes rim adipocytes	– Lymphocytes rim adipocytes – Histiocytes may be present
Cellular types	– Majority of CD163+ histiocytes – Some CD8+ T-cells	– Lymphoid follicles with numerous plasma cells, some with germinal center formation – Few histiocytes and CD8+ T-cells – Can have clusters of CD123+ plasmacytoid dendritic cells	– Majority of CD8+ T-cells with monoclonal α/β TCR – Some histiocytes – Rare plasma cells
Cellular morphology	– Often normal, but may exhibit atypia	– Often normal, but may exhibit atypia	– Atypia
TCR clonality	– Usually polyclonal	– Usually polyclonal	– Usually monoclonal
Treatment	– Glucocorticoids – Calcineurin inhibitors – IL-1 blockade	– Glucocorticoids – Hydroxychloroquine – Mycophenolate	– No HLH, 1st line: – Systemic immunosuppressive agents (glucocorticoids, calcineurin inhibitors, methotrexate) – With HLH and/or failed 1st line: – Multiagent chemotherapy

CHP, Cytophagic histiocytic panniculitis; *LP*, lupus panniculitis; *SPTL*, subcutaneous panniculitis-like T -cell lymphoma; *HLH*, hemophagocytic lymphohistiocytosis; *SLE*, systemic lupus erythematosus; *TCR*, T-cell receptor; *IL-1*, interleukin-1.

replaced with tacrolimus, and steroids were successfully tapered. She was transitioned to adult care and had 2 recurrences of nodules, attributed to discontinuing tacrolimus during pregnancy. Low-dose methotrexate was started without disease recurrence. Continued response was consistent with diagnosis of CHP; repeat biopsy of recurrent lesions was not performed for histologic confirmation.

DISCUSSION

Diagnosis of CHP is challenging due to the spectrum of presentations and substantial histopathologic overlap with LP and SPTL. These entities can manifest with isolated cutaneous nodules, rendering them difficult to distinguish based on clinical features alone, although CHP and SPTL are more likely to involve systemic manifestations than LP. CHP and SPTL in particular appear histologically similarly, with lymphocytes rimming adipocytes and "bean-bag cells" [1,3,5]; therefore, histology alone cannot distinguish the two. We propose that for panniculitis of unclear etiology, immunophenotypic, and genetic profiling coupled with supportive clinical features guide diagnosis. Assessment of lymphocytic clonality status can distinguish SPTL from CHP and LP; monoclonal TCR gene rearrangement suggests SPTL, whereas benign polyclonal gene rearrangement is typically seen in CHP and LP.[5,6] In both patients, TCR polyclonality strongly lowered the likelihood of SPTL.

After excluding SPTL, CHP and LP can be distinguished by clinical and histologic features.

While CHP can present with isolated nodules, it can also involve mild or severe systemic symptoms, even progressing to HLH.[1] In contrast, LP is usually an isolated form of chronic cutaneous lupus erythematosus, only occasionally overlapping with systemic symptoms of SLE.[7,8] Histologically, CHP demonstrates histiocytic and T-lymphocyte predominance, whereas LP has fewer histiocytes and T-cells, with the majority of plasma cells; therefore, histiocytic predominance favors a diagnosis of CHP. While both CHP and LP usually have normal cellular morphology, the pathogenic cells in CHP may display atypia[1,9,10] (Table II).

We propose that immunogenetic profiling of panniculitis tissue as a mode of assessing clonality status, combined with clinical context, is essential for diagnosis and treatment of CHP. CHP can be considered a specific clinical-pathologic entity in cases of indolent nodular lesions after excluding LP and SPTL by clinical features, histopathology, immunophenotyping, and genetic profiling. However, with advances in immunophenotyping, it is possible that patients previously diagnosed with CHP may in fact have SPTL or other panniculitis-like T-cell lymphomas. Given the substantial overlap between these entities, clinical and histopathologic re-evaluation should be continued in patients diagnosed with CHP with concerns for malignant transformation or for persistent, progressive, or recurrent lesions.

Conflicts of interest

None declared.

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