A young woman presented with panniculitis, fever and blood cytopenias, later going on to develop hemophagocytic lymphohistiocytosis. Further evaluation revealed the presence of subcutaneous panniculitis like T-cell lymphoma (SPTCL). With this case we present an approach to panniculitis, a commonly encountered skin manifestation with a wide range of differentials. We discuss the close similarity between lupus erythematosus panniculitis (LEP) and lymphoma.

**Abstract**

A young woman presented with panniculitis, fever and blood cytopenias, later going on to develop hemophagocytic lymphohistiocytosis. Further evaluation revealed the presence of subcutaneous panniculitis like T-cell lymphoma (SPTCL). With this case we present an approach to panniculitis, a commonly encountered skin manifestation with a wide range of differentials. We discuss the close similarity between lupus erythematosus panniculitis (LEP) and lymphoma.

**Introduction**

Lupus erythematosus panniculitis and subcutaneous panniculitis-like T cell lymphoma are close differentials. SPTCL is a rare tumor, which can mimic the former connective tissue disease.

**Case Report and Discussion**

A 23 year old woman presented to our outpatient department with a 4 month history of subcutaneous nodules. The first two had appeared in the left cheek and the right thigh, later going on to involve the abdominal wall and the lower back. They were only mildly painful, stayed for 2 to 3 weeks at a time and then waned off, only to appear at other places. Fever of moderate grade had begun 6 weeks before presentation. She had received antibiotics without appreciable benefit. There was no history of joint pain or swelling, breathlessness or chest pain, jaundice, oral ulcerations or hair loss. There was no bony pain or bleeding from any site. She had lost 3 kilograms in weight. In the past, she had had two spontaneous abortions at 2 months of gestation and had no children. Menstrual cycles were regular. Examination demonstrated tachycardia with a heart rate of 100 per minute and with a large volume pulse. She was pale. The left cheek showed atrophy (Figure 1). Palpation of the skin revealed deep-seated plaques with irregular diffuse outlines, approximately 2 cms x 2 cms over the front and back of the abdominal wall, which were mildly tender. The skin overlying the limbs and chest wall was normal. No superficial lymph nodes were palpable. Auscultation of the chest revealed vesicular breath sounds while the rest of the systemic examination was normal.

What were the lesions? What can be likely differentials? Deep-seated tender skin lesions signify inflammation of the subcutaneous fat, or panniculitis. The causes of panniculitis span a spectrum of disorders including inflammatory, infectious, traumatic, deposition diseases and malignancy. The most common cause is erythema nodosum, often secondary to underlying systemic causes such as streptococcal infection, inflammatory bowel disease and sarcoidosis. EN is self-limiting, does not produce scarring and is typically located on the shins. History and physical examination can help in narrowing down differentials: ulceration is suggestive of vasculitis and erythema induratum, while atrophy is characteristic of lupus panniculitis. The site of the lesions can provide important diagnostic clues with a few causes preferentially involving specific locations (Table 1).

**Table 1: Causes of panniculitis as per site of lesions**

<table>
<thead>
<tr>
<th>Location</th>
<th>Possible causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limbs</td>
<td></td>
</tr>
<tr>
<td>(most common)</td>
<td>Shins</td>
</tr>
<tr>
<td></td>
<td>Erythema nodosum</td>
</tr>
<tr>
<td></td>
<td>Calves</td>
</tr>
<tr>
<td></td>
<td>Erythema induratum</td>
</tr>
<tr>
<td></td>
<td>Medial leg</td>
</tr>
<tr>
<td></td>
<td>Stasis panniculitis</td>
</tr>
<tr>
<td></td>
<td>Thighs, buttocks</td>
</tr>
<tr>
<td></td>
<td>Alpha-1 antitrypsin deficiency</td>
</tr>
<tr>
<td>Upper limbs</td>
<td></td>
</tr>
<tr>
<td>(along with face, upper trunk)</td>
<td>Lupus panniculitis</td>
</tr>
<tr>
<td>Forearms</td>
<td>Sarcoidosis</td>
</tr>
</tbody>
</table>

Histologically, panniculitis is characterized by inflammatory infiltrate either within the fat lobules (Lobular panniculitis) or in the dividing septae (septal panniculitis). Lobular panniculitis may also be a manifestation of connective tissue diseases such as lupus, vasculitis, malignancies, deposition diseases and enzymatic destruction as in pancreatitis.

Lupus erythematosous panniculitis (LEP), described by Kaposi in
1883 can have a variable age of presentation. Persistent lipoatrophy is a characteristic feature, sometimes allowing retrospective diagnosis. (1) LEP may be the only manifestation of disease and is associated with systemic lupus erythematosus (SLE) in 10-42% of cases. (2) It has been described along with other autoimmune diseases such as rheumatoid arthritis and Sjögren’s syndrome. In our patient, involvement of the face with lipoatrophy and the trunk made LEP our first differential. Lymphomas and other malignancies can present with panniculitis, which may closely mimic connective tissue disease.

Case details-continued: Blood investigations from the referring hospital showed anemia with a hemoglobin of 9.6 g% with normocytic, normochromic picture on peripheral smear, leucopenia (TLC= 3400/mm³) with lymphopenia (15% lymphocytes). Erythrocyte sedimentation rate was raised (91 mm/hour), and LDH was raised at 2444 U. Blood chemistry showed transaminitis (AST 212 U, ALT 66 U/dl), albumin:globulin ratio reversal (albumin 2.7 g%, globulin 5.2 g%) with normal renal function. Antinuclear antibodies (ANA) were negative by immunofluorescence. Complement levels were raised (C3= 69 mg/dl, C4 30 mg/dl). Anti-β2gp1 antibodies were raised at 39.2, while anticardiolipin antibodies (IgG and IgM) were negative. HIV ELISA was nonreactive. Blood cultures were sterile.

A skin biopsy and bone marrow biopsy were performed. Her fever responded well to nonsteroidal anti-inflammatory drugs (Naproxen). She wanted to return home for some family engagements, and was discharged pending the biopsy reports.

While the report was still awaited, she returned to the emergency section of this hospital complaining of black tarry stools mixed with fresh red blood without abdominal pain or hematemesis. Examination revealed tachycardia and hypotension, which responded to crystalloids. She had pallor and had icterus. Her skin lesions on the abdomen had acquired a hemorrhagic appearance (Figure 2). Laboratory tests showed a fall in hemoglobin (6.6 g%), thrombocytopenia (23000/mm³) and leucopenia (1500/mm³, with 80% neutrophils). Coagulation parameters were deranged: Prothrombin time (PT) was prolonged with an international normalized ratio (INR) of 2.3, and Activated partial thromboplastin time (APTT) was prolonged by 24 seconds as compared to control. Liver transaminases were raised (AST 1493, ALT 418). She was given packed red blood cells, random donor platelets and fresh frozen plasma. With these measures, GI bleeding stopped.

What could have been the possible cause of this acute presentation?: The patient had evidence of worsening cytopenias, coagulopathy and liver function derangements. Differentials included disseminated intravascular coagulation (due to possible underlying sepsis), acute liver failure and hemophagocytic lymphohistiocytosis (HLH). Blood cultures were sent. ESR dropped to 12 mm/hour. Serum ferritin and serum triglycerides were raised at 16400 micrograms/L and 539 mg/dl respectively. Although it is difficult to differentiate between these syndromes, a high ferritin level, raised LDH pointed towards the diagnosis of HLH.

What is hemophagocytic lymphohistiocytosis?: Hemophagocytic lymphohistiocytosis is a potentially life-threatening condition due to abnormal and excessive activation of macrophages and NK cells, resulting in tissue destruction. It presents with fever and organ damage. It presents with organ dysfunction including liver and CNS, cytopenia and coagulation abnormalities. High ferritin levels are common with most patients having levels more than 500 micrograms/L and 25% having levels >10000. It can be associated with rheumatologic diseases, chiefly Systemic onset juvenile arthritis and SLE, when it is termed macrophage activation syndrome (MAS). A survey of adult HLH patients showed that 50% were associated with malignancy with lymphoid malignancy being the most common cause, especially T, NK cell lymphomas and leukemias.

The association of panniculitis and HLH has been documented. The three chief possibilities include LEP, SPTCL and cytopathic histiocytic panniculitis. The latter is a rare disorder consisting of lobular panniculitis, fever, organomegaly and acute liver failure. Differentiating between these relies upon testing for ANA and findings on skin biopsy. A case series showed 95% patients with lupus panniculitis had positive ANA, albeit in low titres.

Case details-continued: Reports of the biopsies done in the earlier admission were obtained. Skin biopsy showed lobular and septal infiltrate by atypical lymphoid cells, reactive histiocytes and fat necrosis. There was adipocyte rimming by tumour cells. There was periadnexal infiltration, but no vasculitis. Immunohistochemistry revealed 90% of the cells positive for CD3, a marker for T cells. These findings were consistent with Subcutaneous panniculitis like T cell lymphoma. (Figures 3 and 4) The Bone marrow aspirate showed adequate lymphocytes (8%) and mild plasmacytosis. Bone marrow biopsy did not demonstrate any lymphomatous infiltrate or evidence of hemophagocytosis.

Confusion between LEP and SPTCL can persist even on biopsy. Vacuolar rimming with cells can be seen in LEP as well but includes plasma cells and histiocytes in the infiltrate. The
The patient was initiated on pulse methylprednisolone for HLH. A chemotherapy regimen was planned after consulting the Department of Hematology. After transfusion platelet count improved to 56000 and INR reduced to 2.1. However on day 3 of her admission she developed an convolution with altered sensorium, bradycardia and hypertension. Emergency CT scan revealed a large intracranial hemorrhage (Figure 5). She rapidly deteriorated thereafter and despite resuscitative efforts and mechanical ventilation, expired within 4 hours of this acute event.

What is the clinical behavior of Subcutaneous panniculitis like T cell lymphoma?: Subcutaneous panniculitis like T cell lymphoma is a rare form of Non-Hodgkin’s lymphoma presenting as multiple subcutaneous nodules or indurated plaques, which do not ulcerate. While the legs constitute the most common site, they are also known to occur on arms, the trunk and the face. As seen in our patient, they can have a waxing and waning course in the early course, leaving behind areas of lipoatrophy on healing.9 Due to this and its resemblance to panniculitis of other etiologies, it is often diagnosed late, with a median delay of seven months in one case series.10 SPTCL is usually limited to the subcutaneous tissue; lymphnode, bone marrow and internal organ involvement is rare. Two different subgroups were identified based on prognosis: 75% patients with α/β type of T cell lymphoma had an indolent course, while 25% with γ/δ type had a more progressive course with development of HLH in 50%. The EORT classification separated the latter into an independent provisional entity of γ/δ lymphoma.10 TCR typing was not done for our patient, and it seems possible that she could have had the γ/δ type.

Learning Points

1. The etiology of panniculitis can be narrowed down by a deep skin biopsy including the subcutaneous fat
2. Lupus erythematosus panniculitis and subcutaneous panniculitis-like T cell lymphoma form close differentials of each other, both clinically as well as histologically.
3. Demonstration of cellular atypia and monoclonality by the presence of TCR rearrangements in the tumour cells clinches the diagnosis

4. Hemophagocytic lymphohistiocytosis (HLH) must be suspected if a patient with panniculitis develops worsening cytopenia and coagulation abnormality and treated aggressively.

5. The presentation of HLH portends worse prognosis in these patients.

Acknowledgements

We would like to thank the Department of Pathology, SGPGIMS Lucknow for histopathologic slides.

References