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# Bullous pemphigoid and cholestatic hepatitis associated with Castleman's disease

## Castleman hastalığı ile ilişkili kolestatik hepatit ve büllöz pemfigus

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*The case of a 21-yr-old woman admitted with a two-week history of icterus, fever, multiple peripheral lymphadenopathy and pruritic eruption is presented. A full evaluation including computed tomography, endoscopic retrograde cholangiography, liver, skin and lymph node biopsies and biochemical tests confirmed the diagnosis of multicentric Castleman's disease (angiofollicular lymph node hyperplasia). All symptoms improved within four weeks of commencing prednisone therapy. Castleman's disease should be considered in the differental daignosis of cholestatic hepatitis and buttons pemphigoid.*

Key words: Castleman's disease, bullous pemphigoid.

*Sarılık, ateş, çok sayıda periferal lenfadenopati ve pirüritik erupsiyonlarla başvuran, 21 yaşında kadın hasta. Semptomları başvurudan 2 hafta önce başlamış. Bilgisayarlı tomografi, endoskopik retrograd kolanjiografi, karaciğer, deri, lenf nod biyopsileri ve biyokimyasal bulgular sonucunda, multisentrik Castleman Hastalığı (CH) (anjiofolliküler lenf nod hiperplazisi) tanısı konuldu. Tüm semptomlar prednisolon başlandıktan sonra 4 hafta içinde düzeldi. CH kolestatik hepatit ve Büllöz Pemfigusun nedenlerinden biri olarak göz önünde bulundurulmalıdır.*

Anahtar kelimeler: Castleman hastalığı, büllöz pemfigoid.

## INTRODUCTION

Castleman's disease (CD) is rare and usually benign condition of unknown etiology resulting in extensive lymphoid proliferation (1,2). Jaundice has not been reported in CD, and there are only few case reports of bullous pemphigoid (3,4). We report the first case of CD associated with cholestatic hepatitis and bullous pemphigoid.

## CASE REPORT

A 21-yr-old woman was admitted to our hospital in July, 2001 for evaluation of fever, jaundice and lymphadenopathy (LAP). The patient had been well until June, 2001, when she began to suffer from fever, nausea, night sweats, weight loss and malaise. On the following day, she developed diarrhea and jaundice accompanied by pruritus, abdominal distension, lymphadenopathy and pruritic eruption. She had expenenced amenorrhea for four months prior to admission.

The patient had never had a blood transfusion and she denied the use of alcohol, intravenous drugs or any other medication. There was no history of any toxic enviromental exposure.

Physical examination revealed extensive tense bullae with scattered lower and upper extremities. There was no Nikolsky sign. Abdominal examination showed mild tenderness to palpation in the right upper quadrant and there was moderate ascites on abdominal percussion. There was no splenomegaly and cutaneous spider. Breath sounds were decreased on lower thoracic auscultation. There was mild edema of the lower extremities and there were multiple bilateral inguinal and axillary lymphadenopathy (LAP), 1.5cm-2 cm. in size.

Ultrasonography (USG) of the upper abdomen showed ascites an enlarged liver (the span in the

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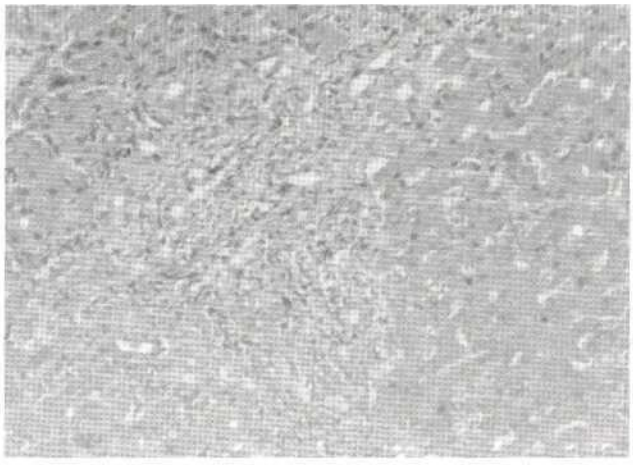

**Figure I.** Histologic examination of liver shows normal lobular architecture with moderate lymphocytic infiltration within portal triad. The interlobular biliary ducts is intact. There is a remarkable hepatocanalicular bile stasis. Hematoxylin and eosin, X200.

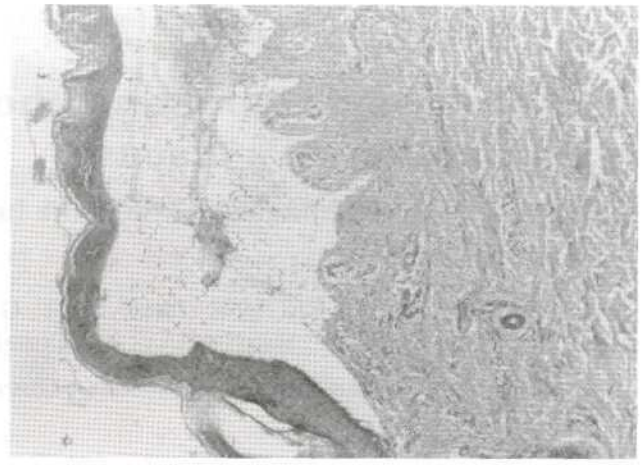

**Figure 2.** The punch biopsy from skin reveals profound tissue eosinophilia, dermoepidermal separation, and eosinophilic spongiosis consistent with bullous pemphigoid. Hematoxylin and eosin, X100

right midclavicular line was 15 cm), with normal gallbladder and nondilated intrahepatic and extrahepatic biliary ducts. Computerized tomography showed LAP at the level of the portahepatis, bilateral axillary inguinal LAP, pleural effusion, ovarian cysts (5cm diameter in the right ovary and 2.5 cm in the left ovary), mild hepatomegaly, and ascites. Endoscopic retrograde cholangiography (ERG), and doppler USG of the porto-splenic and hepatic vein were normal. The results of diagnostic upper endoscopy, echocardiography, whole body bone scanning and barium contrast radiography of the colon and small intestine were normal.

**Table 1.** Laboratory data of the patient on admission

| | |
|---|---|
| *Hemogram* | |
| Wbc (K/uL) | 6600 |
| Neu (%) | 50 |
| Hgb (g/dl) | 10 |
| Pit (K/uL) | 90000 |
| PTT (sec) | 14 |
| *Biochemical profile* | |
| BUN (mg/dl) | 40 |
| Creatinin (mg/dl) | 1.6 |
| Na (mEq/L) | 136 |
| K (mEq/L) | 4.2 |
| Conjugated Bilirubin (mg/dl) | |
| ALP (U/L) | 414 |
| Y-GGT (U/L) | 48 |
| Total protein (g/dl) | 5.1 |
| Albumin (g/dl) | 2.3 |
| Amylase (U/L) | 64 |
| LDH (U/L) | 847 |
| Fe (ug/dl) | 137 |
| TIBC (ug/dl) | 184 |
| Uric acid (mg/dl) | 8.6 |
| Calcium (mg/dl) | 7.3 |
| TSH (uIU/ml) | 1.61 |
| *Acute-phase reactants* | |
| ASO (Ul/ml) | 165 |
| CRP (mg/dl) | 21 |
| ESR (mm/h) | 30 |

Wbc, white blood cells; Neu, neutrophils;Hgb, hemoglobin; Pit, platelets; PTT, prothrombin time; BUN, blood urea nitrogen; ALP, serum alkaline phosphatase; g-GGT, g-glutamyltransferase; LDH, serum lactate dehydrogenase; Fe, iron; TIBC, total serum iron-binding capacity; hTSH, thyroid-stimulating hormone; C-reactive protein; ESR, erythrocyte sedimentation rate

The laboratory profile on admission showed serum bilirubin 8 mg/dl, serum alanine aminotransferase 96 IU/L, serum aspartate aminotransferase 160 IU/L, serum alkaline phosphatase 404 IU/L, serum gama-glutamyltransferase 58 IU/L, serum albumin 2.3 g/dl and interleukin-6 54 pg/ml. The other laboratory profiles are presented in Table 1. Urinalysis were normal and Bence-Jones protein was negative. The serum ceruloplasmin and b2 microglobulin level was within normal range. Tests for hepatitis B surface antigen and core antibody, hepatitis A immunoglobulin M antibody, cytomegalovirus immunoglobulin M antibody, hepatitis C antibody, hepatitis E immunglobulin G antibody, herpes simplex viruses (HSV-1 and HSV-2) immunoglobulin G and M antibody were negative. Tests for brucella, salmonella, and toxoplasma antibodies were also negative. In the other immunological laboratory profiles; rheumatoid factor, VDRL, antinuclear antibody test, anti-Ro, anti-La, antibody to double-strand DNA test, antimitochondrial antibody, smooth muscle anti-

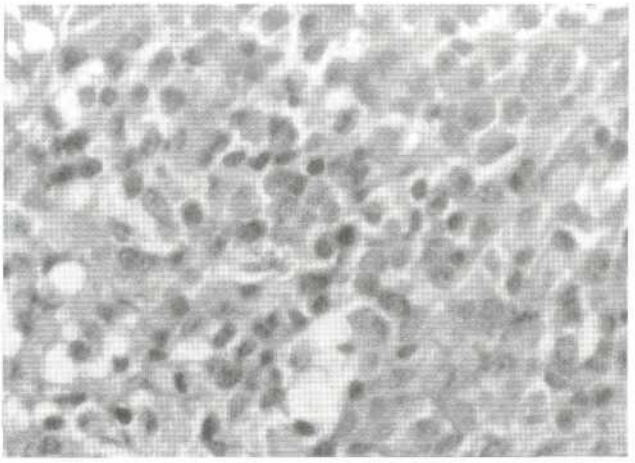

**Figure 3.** Finding of lymph nodes biopsies show follicular hyperplasia with prominence of germinal centers and significant interfollicular plasmacytosis, consistent with the plasma cell type of Castleman's disease. Hematoxylin and eosin, X400

body, antigliadin antibodies IgA and IgG, and anticardiolipin antibodies IgM and IgG were negative. Levels of tumor markers for the ovary were normal. Findings from serum protein electrophoresis revealed monoclonal IgG-k without associated hypogammaglobulinemia, suggesting a benign monoclonal gammopathy. Quantitative IgG, IgA, and IgM test results were unremarkable. There were no neutrophils or lymphocytes in ascitic and pleural fluid and serum-ascites albumin gradient was 0.8. Cultures obtained from ascites, blood, pleural fluid samples were found to be negative for aerobic and anaerobic microorganisms and Mycobacterium tuberculosis. Stool examination for amebiasis, parasite eggs, and toxin A for Clostridium difficile were negative. Leptospira agglutination test was negative.

A percutaneous liver biopsy, skin biopsy, (biopsy from axillary and cervical lymph nodes, bone marrow aspiration and biopsy and rectal biopsy were performed. Amyloid was not detected in any biopsy sample. Histologic examination of the liver showed normal lobular architecture with moderate mononuclear cell infiltrate within the portal triad. The interlobular biliary ducts were intact. There was a remarkable hepatocanalicular bile stasis. (Figure 1). Results of punch biopsy from skin revealed profound tissue eosinophilia, dermoepidermal separation, and eosinophilic spongiosis consistent with bullous pemphigoid (Figure 2). Direct immunofluorescence findings revealed 1+ to 2+ linear dermoepidermal-junction C3 deposition. Autoantibodies against the epidermal site of salt-split skin basement membrane were detected using specific anti-human IgG conjugate. Bone marrow biopsy analysis revealed hypercellularity. Findings of lymph nodes biopsies showed follicular hyperplasia with prominence of germinal centers and significant interfollicular plasmacytosis, consistent with the plasma cell type of CD (Figure 3).

The patient's condition improved with treatment initiation of oral prednisone lOmg daily. At discharge, she was given 60 mg of prednisone daily, 150 mg of azathioprine daily and 20 mg of famotidine twice daily. She remained stable on treatment of 50 mg of azathioprine daily following tapering and discontinuation of the prednisolone. A follow-up CT scan and physical examination revealed no residual lymphadenopathy, ovarian cyst, ascites or pleural effusion. All abnormal laboratory profiles had improved.

## DISCUSSION

Castleman' s disease is a rare and usually benign condition of unknown etiology resulting in extensive lymphoid proliferation. It is classified into three histologic types: the hyaline-vascular type, the plasma-cell type and hyaline-vascular plasma cell type. It is also categorized into two clinical types: localized and multicentric (1,2). The plasma cell type is most often abdominal, and includes fever, fatigue, weight loss, hypergammaglobulinemia, anemia, leukocytosis, thrombocytosis, and hypoalbuminemia. Multicentric CD presents with diffuse lymphadenopathy and generally has an aggressive, fatal course (5). It is associated with malignancies such as lymphoma and Kaposi sarcoma (38%) and human herpesvirus type 8 (6).

This case is unusual in that the patient had the rare multicentric plasma-cell type of CD without an aggressive, fatal course. Although the presence of malignancies, such as lymphoma, cause an aggressive course, the reason for this is generally associated with presence of comorbid disease, such as hypothyroidism and neuropathy (5,7). In a recent study, the clinical symptoms were associated with a high level of interleukin-6 (8). Although cases with pleural effusion, ascites, impaired liver and renal function tests and the presence of systemic symptoms (fever, night sweats, malaise/weakness, anorexia/nausea or vomiting, weight loss) are known, no cases with jaundice and amenorrhea have been reported. The proba-

ble cause of pleural and peritoneal fluid collection is hypoalbuminemia. The development of bullous pemphigoid and cholestatic hepatitis in patients with CD may be related to underlying immune dysfunction. The pathogenesis is thought to be secondary to a reactive inflammatory process caused by autoimmune phenomenon, antigenic stimulation, or infection.

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