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Case Report

Internal Medicine Section

Sarcoidosis and Primary Biliary Cholangitis- An Overlap

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ABSTRACT

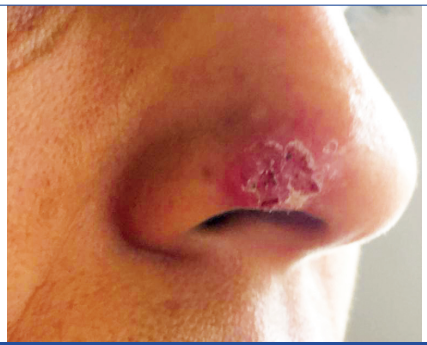
Primary Biliary Cholangitis (PBC) is a chronic progressive autoimmune cholestatic liver disease. Sarcoidosis is a multisystem chronic granulomatous disease. Both diseases are known to affect the liver causing granulomas. Sarcoidosis commonly involves the skin while PBC is associated with autoimmune skin disorders. Diagnosis of PBC requires biochemical, serological and histological confirmation. Steroids are used in the treatment of sarcoidosis. The role of steroids in the treatment of PBC is not completely established. In this case report, authors present the case of a 31-years-old female diagnosed as sarcoidosis based on granulomatous lesions in skin biopsy with concurrent PBC diagnosed on basis of serology and liver biopsy.

Keywords: Autoimmune liver disease, Chronic granulomatous disease, Liver granuloma, Skin plaque

CASE REPORT

A 31-years-old female presented to the General Medicine Outpatient Department with a history of generalised non itchy hyperpigmentation of the skin with skin lesions over the nose and forehead since six months. She had intermittent low-grade fever, weight loss and breathlessness on exertion which was not associated with palpitations, chest pain or syncope since six months. She had hair loss since past six months. Patient also had a prior three years history of frontal headache associated with nausea and vomiting. There was no history of athralgia, skin tightening, Raynaud's phenomenon, pain abdomen, jaundice, oliguria, haematuria or goitre. She had a past history of hypothyroidism and was on supplementation which was discontinued for unknown reasons one month before presentation. There was no other significant illness in the past in the patient or the family. There was no history of chronic drug intake or exposure to heavy metals or history of promiscuous behaviour.

On examination, the patient was poorly nourished. She had multiple well defined, erythematous infiltrative plaques over the right ala of nose and forehead, 2 cm above left supra orbital ridge and 6 cm above left supra orbital ridge. There were hyperpigmented patches over the extremities and trunk [Table/Fig-1]. There was no peripheral nerve thickening.



[Table/Fig-1]: Plaques over the face.

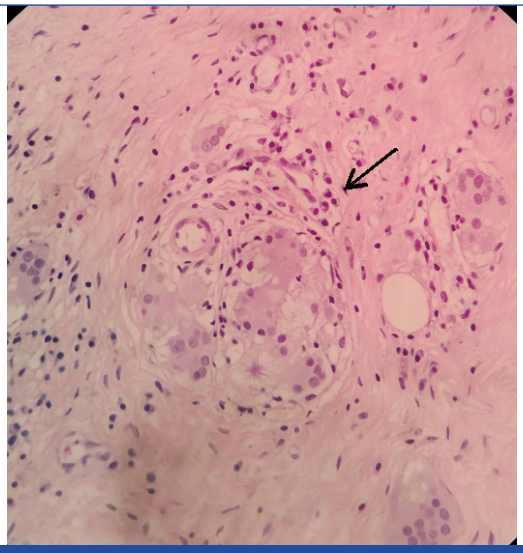
Her pulse was 96 beats per minute in the right radial artery with a weak pulse in the left radial artery. Blood pressure measured in the right upper limb was 170/100 mmHg and the left upper limb was 160/100 mmHg and systolic blood pressure in both lower limbs was equal. She was afebrile and had grade 2 hypertrophied tonsils bilaterally. Fundus showed flame shaped haemorrhages with grade 1 hypertensive retinopathy. Anterior segment of the eye was normal. Cardiovascular system examination revealed a loud Pulmonic Valve Closure (P2) in the pulmonary area. Nervous system examination was normal.

On blood investigation, there was mild anaemia, elevated Erythrocyte Sedimentation Rate (ESR), mildly elevated serum creatinine, and albuminuria. Total protein was elevated with hyperglobulinemia. Liver function tests showed elevated alkaline phosphatase and gamma glutyamyl transferase [Table/Fig-2]. Electrocardiography (ECG) and Echocardiogram (ECHO) showed left ventricular hypertrophy.

Parameters	Value
White blood count (cells/cumm)	10,400
Haemoglobin (gm/dL)	10.8
Mean corpuscular volume (fL)	82.3
Mean corpuscular haemoglobin (pg)	26.6
Mean Corpuscular Haemoglobin Concentration (MCHC) (%)	32.3
Platelet count (lac/cumm)	3.09
Peripheral smear	Normocytic Normochromic Anaemia of mild degree
Reticulocyte count (%)	0.5
Erythrocyte sedimentation rate (mm/hr)	117
Serum creatinine (mg/dL)	1.25
Blood urea (mg/dL)	23.54
Urine albumin (mg/dL)	50
Electrolytes	137/3.56/100/9.7
Random blood sugar (mg/dL)	87
Total bilirubin (mg/dL)	0.7
Direct bilirubin (mg/dL)	0.17
Total protein (g/dL)	9.3
Albumin (g/dL)	3.07
Globulin (g/dL)	6.23
Aspartate aminotransferase (U/L)	98
Alanine aminotransferase (U/L)	82
Alkaline phosphatase (U/L)	675
Gamma Glutamyl Transferase (GGT) (IU/l)	204
Spot urine protein: Creatinine ratio	0.76
Serum cortisol (mcg/dL)	10,2
Serum Angiotensin-Converting Enzyme (ACE) Levels (IU/l)	90
Prothrombin time/International normalised ratio/ Partial thromboplastin time (sec)	10.9/0.94/34.9
Iron/Ferritin/Total Iron-Binding Capacity (TIBC)	43 mg/dL/82.3 ng/mL/279 ug/dL
Thyroid stimulating hormone (uIU/mL)	1.71

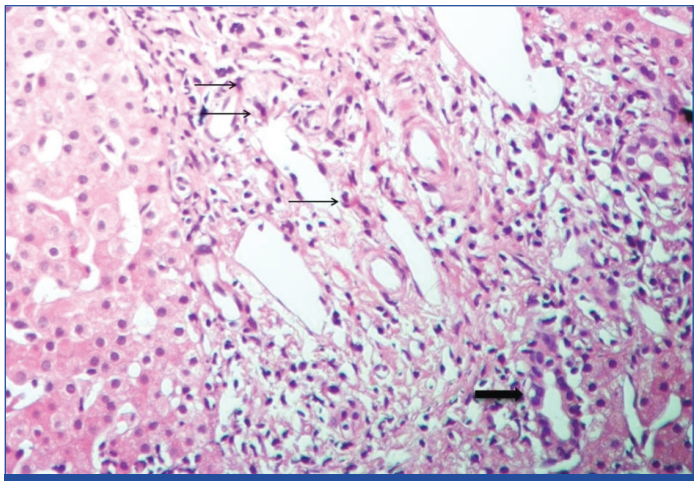
[Table/Fig-2]: Blood investigations.

Antinuclear Antibody (ANA) titres were positive in 1:100 dilution in a perinuclear pattern and Anti Mitochondrial M2 Antibody (AMA-M2) was positive. Chest X-ray showed diffuse nodular opacities in bilateral lung fields. Ultrasound of abdomen showed normal sized liver with heterogenous and mildly course echotexture with normal portal venous architecture. Doppler of left upper limb showed reduced peak systolic flow in left radial artery. Montoux test was negative. Skin biopsy from the lesion over the forehead showed dense non caseating granulomatous infiltrates in the dermis extending into the subcutaneous fat. Granulomas contained epitheloid histiocytes with oval nuclei with variable Langhans giant cells. These findings were suggestive of sarcoidosis [Table/Fig-3].



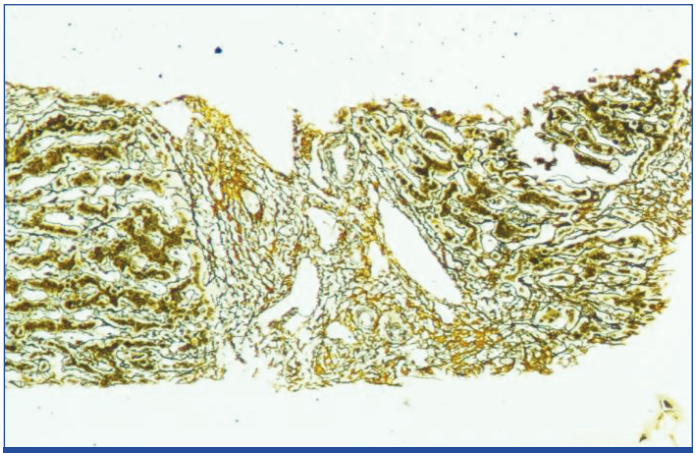
[Table/Fig-3]: Skin biopsy showing features of sarcoidosis. (H&E) X400

Liver biopsy showed predominantly portal based inflammation with involving an occasional bile duct with ductular proliferation. There was moderate fibrosis (Ishak score 3-4/6, i.e., fibrous expansion of portal areas with some areas having occasional and some areas having marked portal to portal bridging as well as portal to central bridging) These features were suggestive of early stages of PBC [Table/Fig 4,5]. Other conditions to be suspected with this histopathological picture are autoimmune cholangitis, autoimmune hepatitis, secondary biliary cholangitis, drug induced liver injury.



[Table/Fig-4]: Liver tissue showing portal lymphocytic inflammation with occasional plasma cells and eosinophils (small arrow) and bile duct showing cytoplasmic vacuolation (Thick arrow), (H&E 20X).

Patient was started on Tab.Ursodeoxycholic (UDCA) acid 600 mg once daily and prednisolone 40 mg/day and other supportive treatment such as Angiotensin-Converting Enzyme (ACE) inhibitors, anti hypertensives and steroid, glycolic acid and tretinoin ointment for local application. She was telephonically followed-up after three weeks and there was improvement in the lesions along with no further fever or weight loss. Follow-up was lost after that.



[Table/Fig-5]: Liver tissue with portal fibrosis, 10X, Reticulin stain.

DISCUSSION

Primary Biliary Cholangitis (PBC) is a chronic progressive autoimmune cholestatic liver disease leading to end stage liver disease. It presents more commonly in females in the fourth and fifth decade of life. It has a prevalence of around 12.9 per 100,000 populations [1]. Fatigue and pruritus are said to be the most common dermatologic presentation of the disease [2]. The first line of therapy includes ursodeoxycholic acid at 13-15 mg/kg. Licensed second line therapy includes obeticholic acid 5-10 mg/day while fibrates and budesonide are used off label [2].

Sarcoidosis is a chronic granulomatous disease affecting multiple organ systems. The prevalence of sarcoidosis in India is 61.2 per 100,000 new cases at a tertiary care center in New Delhi [3]. Pulmonary involvement is most common followed by cutaneous manifestations such as erythema nodosum, lupus pernio and plaques [3]. There is no specific diagnostic criteria for sarcoidosis and is considered as a diagnosis of exclusion. As ACE levels are non specific, histopathological examination of the site showing non caseating epitheloid cell granuloma is confirmatory [3]. Corticosteroids are the first line of therapy while azathioprine and methotrexate act as second line agents for the treatment of sarcoidosis [4]. Derangement in the cell mediated immunity plays a role in the pathogenesis of both the diseases hence both diseases may overlap in their presentation.

PBC can be diagnosed based on three criteria-biochemical abnormalities, serology and histology. It can be diagnosed when two of three criteria are abnormal [5]. Elevation of Alkaline Phosphatase test (ALP) and GGT is the hallmark of biochemical abnormalities whereas Aspartate Transaminase/Alanine Aminotransferase (AST/ALT) ratio of more than one can be used a marker for liver fibrosis [2]. Elevation of serum bilirubin levels occurs as the disease progresses. The hallmark immunological marker is AMA-M2 (E2 subunit) (1:40) positivity which is seen in more than 95% of patients with PBC. It has a sensitivity of about 90% and specificity of 98% [5]. The most common immunofluorescence patterns for observed in PBC are 'nuclear rim pattern' and the 'multiple nuclear dots' pattern [6]. On histology, the hallmark features are chronic, non suppurative cholangitis affecting interlobular and septal bile ducts causing ductopenia with infiltration of plasma cells, macrophages, mononuclear inflammatory cells and presence of epitheloid granulomas [7]. PBC can be seen in association with extrahepatic conditions such Sjogren's syndrome, Raynaud's syndrome and autoimmune thyroid disease but association with sarcoidosis is rare [8]. The skin diseases commonly associated are lichen planus, vitiligo and psoriasis [9].

There have been data of overlap of PBC with sarcoidosis following liver biopsy such as PBC with neurosarcoidosis and hepatic sarcoidosis where hepatic granulomas typical for sarcoidosis and PBC [10]. A population based study showed statistically insignificant association between cases of PBC with hepatic sarcoidosis [11]. This relationship may be attributed to a similar pathogenesis of the two diseases. In sarcoidosis, there is exaggerated immune cell activation by an antigenic stimulus causing macrophages to secrete Interleukin (IL)-1, IL-6 and IL-12 which stimulate Th1 cells. The accumulation

of mononuclear cells is mediated by imbalances in the T cell response with an increase in Th1 and Th17 response and decrease in Treg response. The triggering antigens may be infectious or non infectious agents [12]. Pathogenesis of PBC involves autoreactivity of B-cells and T-cells against the mitochondrial antigens namely the E2 component of the Pyruvate Dehydrogenase Complex (PDC) [13]. On the contrary, there is published data regarding cholangitis mimicking primary billiary cirrhosis in a 52-year-old man with no actual morphological evidence of PBC [14].

Both the diseases are known to have hepatic granulomas. Hepatic granulomas occur in 11-65% of cases of sarcoidosis. They can be differentiated from the granulomas in PBC by being well defined and greater in number. The granulomas of sarcoidosis tend to coalesce in the portal and periportal area without loss of bile ducts. The Cluster of Differentiation 4 (CD4) cells accumulate in the centre of the granulomas in both the conditions whereas the CD8 cells tend to accumulate in the periphery of the granuloma in case of sarcoidosis and around the bile ducts in cases of PBC [15].

Present case report demonstrates that both sarcoidosis and PBC involves similar organ systems and can present in similar ways due to the similar pathogenesis. In a similar case study, a 69-year-old female who presented with pain abdomen, exhaustion and headache was found to have deranged liver function tests, positive AMA-M2, liver biopsy showing granulomatous lesions, elevated ACE levels and was started on treatment with UDCA and prednisolone [10]. Hence, we must investigate for simultaneous presentations of these diseases when presented with hepatic and skin involvement. The treatment modalities also vary in both the diseases. The response of PBC to steroid therapy is not completely established [16].

CONCLUSION(S)

Primary Biliary Cholangitis (PBC) and sarcoidosis are diseases with varied aetiology, similar pathogenesis and affects multiple organ systems. These two diseases can present simultaneously and requires to be managed individually. The distinction between the two diseases based on liver histology is challenging and needs further elucidation with a case series.

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