





Chronic brucellosis with hepatic brucelloma and AA amyloidosis in a patient with autosomal dominant polycystic kidney disease

Arpitha Kollabathula^a, Vikarn Vishwajeet^a , Kirti Gupta^a ,
Suvradeep Mitra^a , Vibhav Sharma^b, Pallab Ray^c , Ashish Bhalla^b

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ABSTRACT

We describe an autopsy case of a 45-year-old male diagnosed with autosomal dominant polycystic kidney disease who presented with complaints of altered sensorium. The autopsy revealed multiple tumor-like masses in the liver, which on histological examination depicted multiple large suppurative granulomas with the presence of variable acid-fast coccobacilli (consistent with *Brucella spp.*). Interestingly, extensive amyloid deposition in multiple organs was noted. To the best of our knowledge, this is the first case of chronic brucellosis causing tumor-like abscesses in the liver accompanied by secondary systemic amyloidosis in a patient with underlying autosomal dominant polycystic kidney disease.

Keywords

Brucellosis; Amyloidosis; Autopsy; Polycystic Kidney, Autosomal Dominant.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by multiple epithelial-lined cysts involving both cortex and medulla, causing massive enlargement of kidneys and renal failure by the fifth to the sixth decade of life.¹ In the present case, ADPKD was complicated by systemic involvement by *Brucella* infection. Brucellosis is a zoonotic disease that may affect almost any organ of the human system, particularly the reticuloendothelial system, including the liver, spleen, bone marrow, and lymph node. Tumor-like suppurative liver abscesses is an infrequent presentation of *Brucella spp* infection and are mainly described in the chronic course of the infection.² Similarly to other chronic infections such as tuberculosis, chronic brucellosis may be an inciting

factor for secondary amyloidosis, as vindicated in this case report. Herein, we describe an unusual case of chronic brucellosis causing tumor-like liver masses in a patient of ADPKD accompanied by AA amyloidosis.

CASE REPORT

A 45-year-old male was brought to the emergency room because of altered sensorium and seizures. On admission, the blood glucose was 15mg/dl, blood pressure of 50/30 mm Hg, respiratory rate of 22/min, and oxygen saturation at room air is 88%. The Glasgow coma scale was E2V1M3, and despite the therapeutic efforts, he expired four hours after

^a Postgraduate Institute of Medical Education and Research, Department of Histopathology. Chandigarh, India.

^b Postgraduate Institute of Medical Education and Research, Department of Internal Medicine. Chandigarh, India.

^c Postgraduate Institute of Medical Education and Research, Department of Medical Microbiology. Chandigarh, India.



the admission. He was diagnosed with hypertension and chronic renal failure due to ADPKD and was on hemodialysis over the past 6 months. He recently attended hospital consultation complaining of diarrhea treated with antibiotics. In that occasion, he was pale, tachycardic but the remaining vitals were normal, and lab work-up revealed anemia and thrombocytopenia while leucocyte count and electrolytes were normal. The creatinine and urea were (2.4mg/dl, reference range [RR]- 0.7 to 1.3 mg/dL) and (72mg/dl, RR- respectively 8-24 mg/dL). Despite adequate measures, he succumbed to his illness.

AUTOPSY PRESENTATION

At the opening of the abdominal cavity, 700 ml of peritoneal fluid was drained. The liver was enlarged, weighing 1480 grams (RR-1000-1200gms). The capsular

and cut surfaces showed multiple nodules ranging from 0.2 to 6 cm. The nodules were grey, soft nodules with central cavitation, eventually with necrosis, mimicking a tumor (Figure 1A). Few small liver cysts were also found. Histologically, these nodules were relatively circumscribed and comprised of suppurative granulomas with central necrosis surrounded by numerous neutrophils, degenerated inflammatory cells and palisading histiocytes. Similar lesions were also found in the spleen, lymph nodes, and bone marrow, albeit less numerous. Also, occasional foci of similar nodules were seen in the lungs, stomach, and pancreas. Periodic acid Schiff's (PAS) and Gram stain failed to reveal any fungal hyphae and bacteria-like organisms, respectively. Modified Ziehl-Neelsen stain demonstrated variably positive pin-point, coccobacilli consistent with the morphology of *Brucella spp*³ (Figures 1B-D).

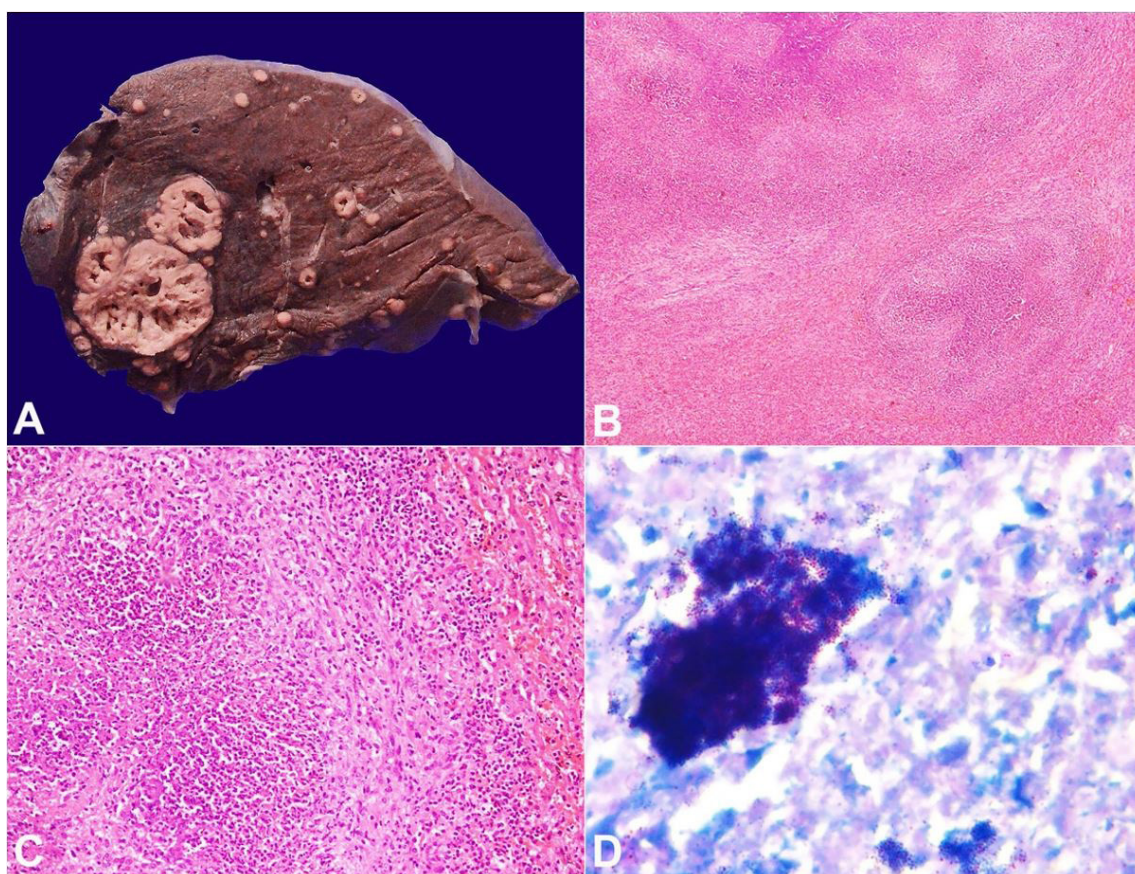


Figure 1. **A** - Gross view of the liver cut surface showing presence of multiple variable-sized nodules (0.2 to 6cm) with soft to firm consistency, some cavitating nodules filled with necrotic material also noted giving a 'tumor-like' appearance; **B-D** - Photomicrographs of the liver; **B** - multiple well-circumscribed areas of suppurative granulomas (H&E, 40X); **C** - suppurative granulomas with central necrosis surrounded by degenerated inflammatory cells and palisading histiocytes (H&E, 200X); **D** - Oil immersion microphotograph from hepatic abscess showing small red coccobacilli in large clumps (Modified Ziehl-Neelsen, 1000X).

Para-aortic lymph nodes were enlarged with central necrotic material (Figure 2A). The nodular lesions in other organs of the reticuloendothelial system, pancreas, lungs, and stomach were histologically similar to the hepatic lesions (Figures 2B, 2C and 3A-C)

Kidneys were massively enlarged, heavy, and together weighed 4.2 kilograms (RR; 150 to 160 grams). The reniform shape was distorted with multiple cysts and measured 28x18x6cm. The cortical and cut surface showed multiple variable-sized cysts (0.2 to 0.5cm) filled with clear to tan color fluid and some with greyish granular material. Septa of variable thickness separated the cysts without any intervening renal parenchyma (Figure 4A). Microscopically, the cysts were defined by flattened to low cuboidal lining epithelium and filled with eosinophilic material (Figure 4B).

Remnants of renal parenchyma were noted in the intervening septa in the form of interstitial fibrosis and hyalinization along with atrophic tubules and few glomeruli (Figure 5A). Notably, these glomeruli showed mesangial expansion with deposition of pale, eosinophilic, acellular amorphous material which on Congo red stain demonstrated congophilia with apple-green birefringence on polarizing microscopy, thus confirming the presence of amyloid (Figure 5B). Amyloid deposition was also seen in arterioles and around tubules. Serum amyloid A showed strong immunopositivity in this material (Figure 5C). Amyloid deposits were negative for antibodies against kappa and lambda.

Besides suppurative granulomas, the pancreas showed few dilated ducts and small cysts in the

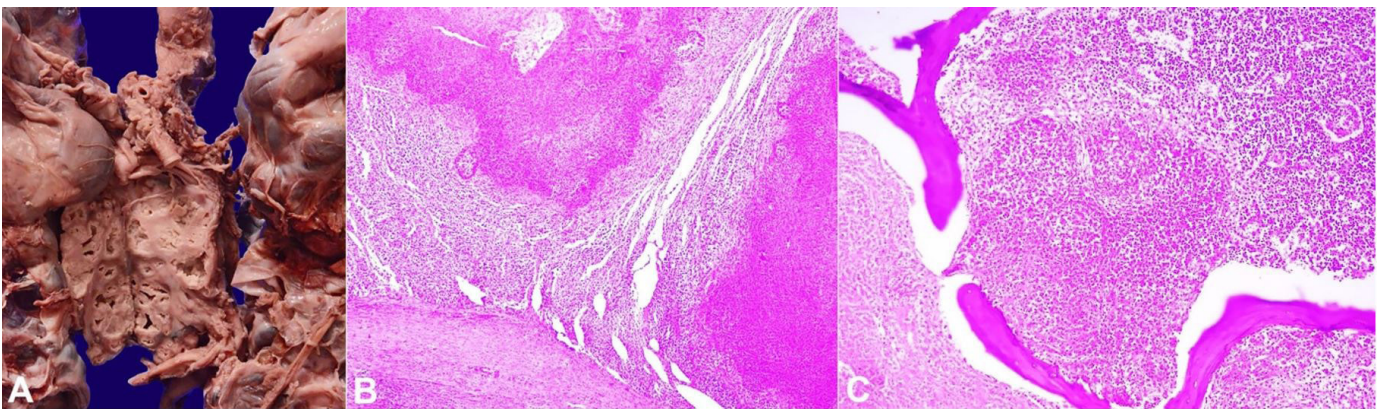


Figure 2. **A** - Gross view of enlarged, matted para-aortic lymph nodes with cavitating lesions filled with necrotic material; **B** - Photomicrograph of the lymph node showing large areas of necrosis surrounded by histiocytes (H&E, 40X); **C** - Photomicrograph showing similar suppurative granulomas in the bone marrow (H&E, 100X).

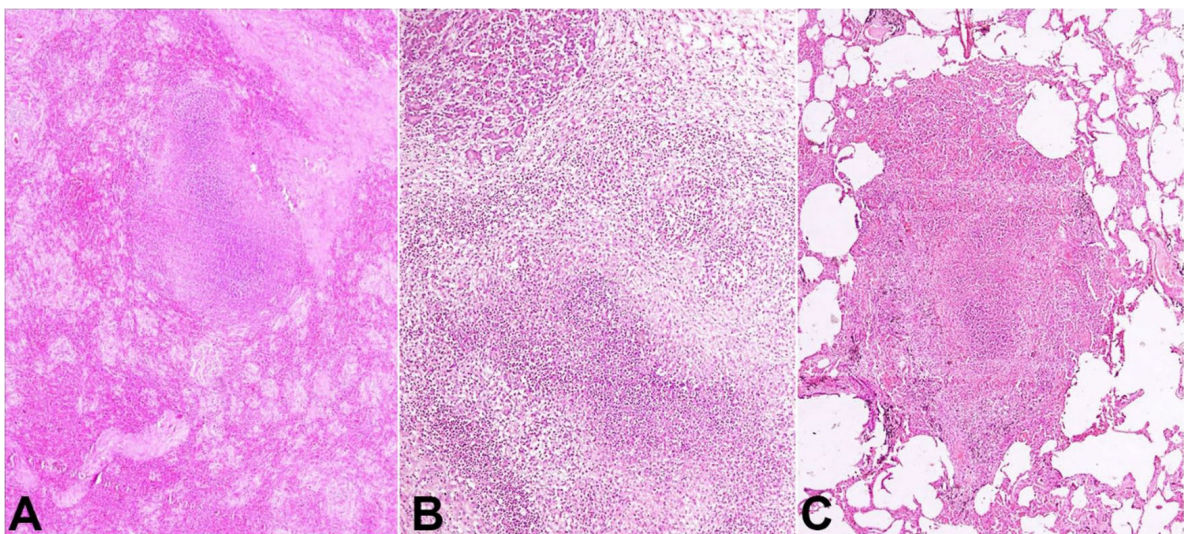


Figure 3. Photomicrographs showing suppurative granulomas in the spleen (**A**, H&E, 100X), pancreas (**B**, H&E, 100X), and lungs (**C**, H&E, 100X).

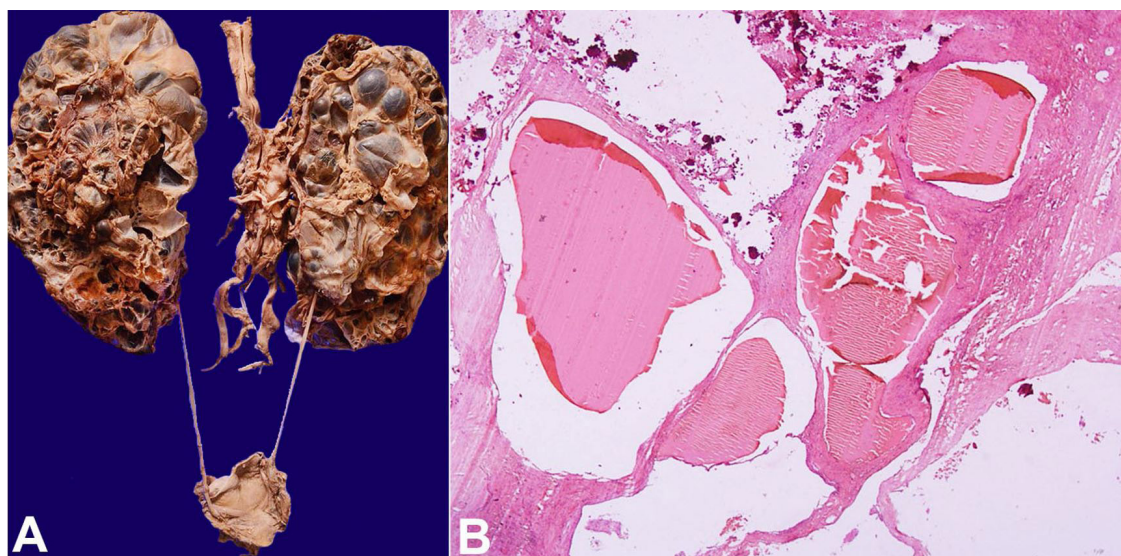


Figure 4. **A** - Macroscopic view of the urinary system showing massively enlarged and heavy kidneys studded with multiple variable-sized cysts filled with clear to tan color fluid and granular material; **B** - Photomicrograph of the kidney showing flattened to cuboidal lining epithelium containing eosinophilic material (H&E, 40X).

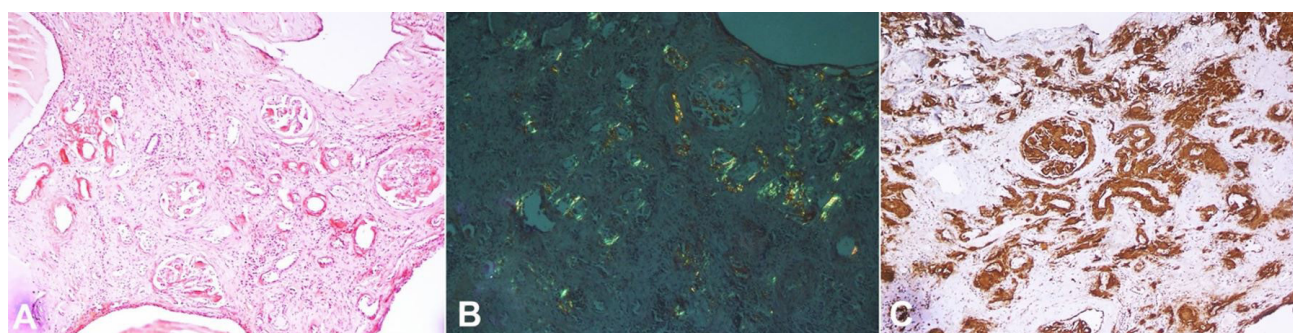


Figure 5. Photomicrographs of the kidney showing in **A** - Residual renal parenchyma noted in septa with interstitial fibrosis and hyalinization along with atrophic tubules and scattered glomeruli. Glomeruli showed mesangial deposition of pale eosinophilic amorphous acellular material (H&E, 200X); **B** - Polarizing microscopy of Congo red stain section showing characteristic apple-green birefringence in areas with congophilia. (Congo red, 200X); **C** - Amyloid immunopositive deposits for antibodies against serum amyloid A protein (immunoperoxidase, 200X).

parenchyma which were filled with eosinophilic material. Mild interlobular fibrosis was also seen. The heart weighed 312g (RR; 270-320 g). The epicardial surface showed fibrinous tags. The left and right chambers, including valves were unremarkable; however, microscopic examination revealed extensive deposition of amyloid interspersing the myocardiocytes and blood vessels (Figure 6A and 6B).

In addition, evidence of old healed myocardial infarction in the form of fibrosis was noted. Scattered foci of dystrophic calcification were seen. Coronary arteries showed partial to near-total occlusion by atheromatous plaque. The spleen was enlarged

and weighed 280gm (RR; 150-180 g). In addition to suppurative granulomas, the trabeculae and periarteriolar sheath showed extensive deposition of amyloid (Figure 7A). Amyloid deposition was also detected in adrenal glands, liver and parenchymal blood vessels of the pancreas (Figures 7B and 7C) and blood vessels of the small intestine and large intestine.

Lungs weighed 754gms (RR; 1000-1100gms) with scattered tiny palpable nodules on the gross examination which were confirmed to be suppurative abscesses on microscopic examination. The remaining organs, including brain, testes, skin, and muscle, did not reveal any significant pathology. In conclusion,

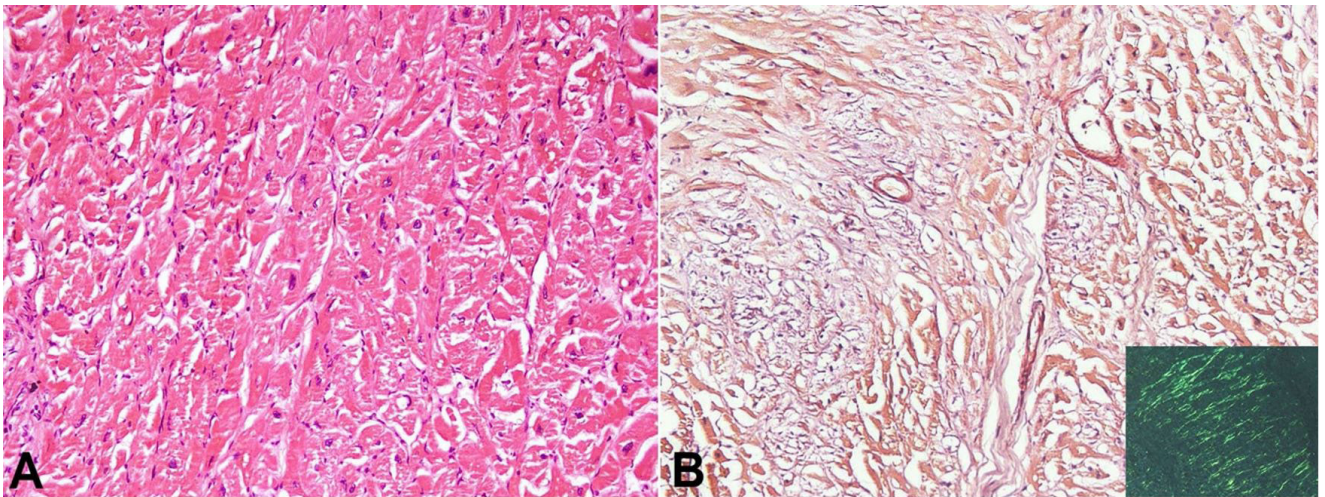


Figure 6. Photomicrographs of the heart showing in **A** - The presence of a pale eosinophilic material in the interstitium and wall of blood vessels (H&E, 100X); **B** - Congo red stain demonstrating congophilia in areas with pale eosinophilic material. Inset shows apple-green birefringence on polarizing microscopy (Congo red, 100X).

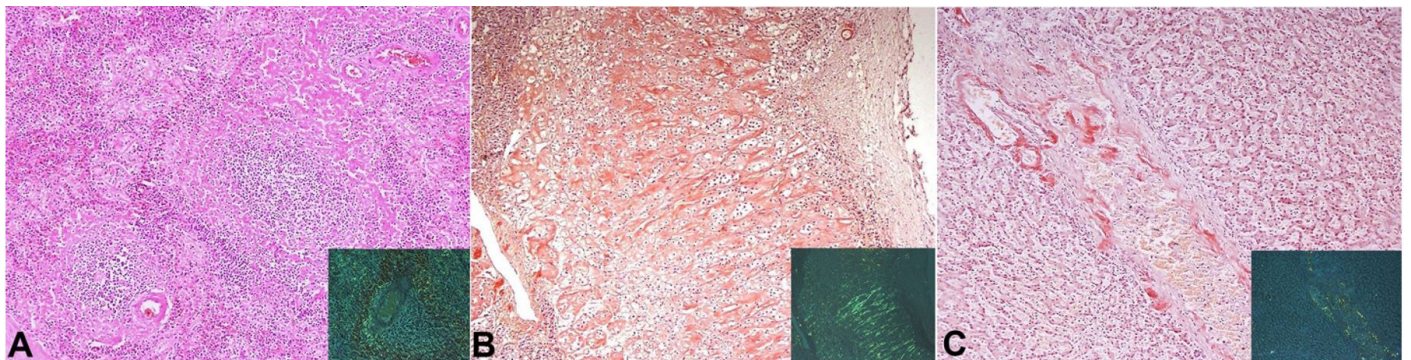


Figure 7. Photomicrographs of the: **A** - spleen with amyloid deposits (H&E and inset Congo red stain, 200X); **B** - adrenal gland (Congo red stain, 200X); **C** - liver (Congo red stain, 200X).

the autopsy findings revealed ADPKD, suppurative granulomas involving liver, spleen, lymph nodes, bone marrow, pancreas, lung, and stomach, consistent with chronic *Brucella* infection, and AA amyloidosis involving heart, adrenal, spleen, liver, kidneys, pancreas and gastrointestinal tract.

CLINICAL DISCUSSION

Brucellosis is the most common zoonosis worldwide, caused by an intracellular bacterium of genus *Brucella*.² It occurs mainly in endemic areas where the infection has yet not been eradicated and mainly affects persons in contact with animals. Six species of *Brucella* are known, out of which four are known to cause brucellosis in humans- *B. abortus*, *B. melitensis*, *B. suis* and *B. canis*.² The transmission of the bacteria to humans occurs via contact with

infected animal parts, consumption of infected milk products or via inhalation of the bacterial containing aerosolized particles. After the infection, the bacteria are phagocytosed by the monocytic-macrophage system and are eliminated, if the inoculum is small. However, if they are not controlled, the phagocytosed bacteria enter the systemic circulation and causes multisystemic disease involving spleen, liver, bone marrow, lymph nodes, nervous, cardiovascular, musculoskeletal, gastrointestinal, dermatological and genitourinary systems. The organism shows preferential involvement of the organs of the reticuloendothelial system (spleen, liver, bone marrow, and lymph nodes).⁴ In the present case, while the postmortem blood culture failed to demonstrate the bacterium, the preferential involvement of the reticuloendothelial system with characteristic gross and histological features coupled

with variable acid-fast coccobacilli strongly favored the diagnosis of *Brucella* as the etiological agent.

Brucella has a wide-ranging clinical manifestation with an acute, subacute, or chronic course. The liver is involved in almost all patients of brucellosis and manifests as hepatomegaly.² 'Brucelloma' is a term given by Davion in 1987⁵ to lesions simulating a tumor. Microscopically, these are characterized by suppurative or necrotizing granuloma with variable admixture with epithelial cells, histiocytes, neutrophils. Parenchymal necrosis, lobular and portal inflammation and sinusoidal cell hyperplasia are other associated features.⁶ Multiple large brucellomas overwhelmingly dominated the liver involvement in the present case on the gross examination, which histologically featured multiple confluent to isolated suppurative granulomas with neutrophil-rich center bordered by histiocytes and epithelioid cells. The hepatic parenchyma at these foci was necrotic. Such type of mass-like hepatic brucelloma are commonly encountered in adults with a chronic form of the disease and are very rare in children with acute brucellosis.^{5,7} Recently, Barutta et al.² have described a single case of hepatic brucelloma and reviewed 41 previously reported cases. The clinical signs and symptoms are often non-specific and may include undulant fever, malaise, weight loss, and upper abdominal pain of insidious onset. Hepatomegaly and splenomegaly are less commonly found in chronic brucellosis. Laboratory investigation often may not show increased aminotransferases; however, a mild elevation of alkaline phosphatase and gamma-glutamyl transferase are noted. Diagnosis usually is based on demonstration of serological positivity and compatible radiological findings and confirmed by the histological pattern of injury or positive culture results.

A second notable feature in the present case was widespread secondary systemic amyloidosis involving heart, adrenal, spleen, liver, kidneys, pancreas, and gastrointestinal tract (GIT). Case reports of association of ADPKD with secondary systemic amyloidosis are on record in the literature (Table 1).⁸⁻¹¹

The inciting event for such amyloidosis in the reported cases is primarily attributed to chronic renal cyst infection in 2 cases, chronic hepatic cyst infection and pulmonary tuberculosis in one case each. AA amyloidosis is well known to be associated with chronic infections and chronic inflammatory conditions.¹² The possibility of dialysis-related amyloidosis (DRA) was not considered as the amyloid was strongly immunopositive for SAA, a marker of secondary amyloid, in contrast to DRA, composed of A β 2microglobulin. Moreover, DRA typically affects the osteoarticular system, unlike the index case showing amyloidosis of the internal viscera.¹³ Brucelloma, as a long-standing smoldering disease could also be the underlying cause for such systemic amyloidosis.

In this case, secondary systemic amyloidosis was noted in multiple organs involving heart, adrenal, spleen, liver, kidneys, pancreas, and gastrointestinal tract. A few case reports have been published in the literature showing the association of secondary amyloidosis and ADPKD (summarized in Table 1). A total of four case reports have documented histological evidence of AA amyloidosis in patients with ADPKD.⁸⁻¹¹ The etiology of amyloidosis was ascribed to chronic renal cyst infections in two cases, chronic hepatic cyst infections in one case and pulmonary tuberculosis in one case.⁸⁻¹¹ AA amyloidosis is well known to be associated with chronic infections and chronic inflammatory states.¹² In the present study, the patient had chronic brucellosis, which may be ascribed

Table 1. Summary of case reports in the literature describing the association of AA amyloidosis with autosomal dominant polycystic kidney disease

Cases	Age/Gender	Etiology of AA amyloidosis	Diagnosis established
Kamimura ⁸	62yr/F	Recurrent hepatic cyst infections	Autopsy
Sar ⁹	39yr/M	Pulmonary tuberculosis	Antemortem
Tsuchiya ¹⁰	66yr/F	Chronic renal cyst infections	Antemortem
Yenigun ¹¹	52yr/M	Infected renal cysts	Antemortem
Index case	45yr/M	Chronic brucellosis	Autopsy

yr = year; M = male; F = female.

to be the cause of AA amyloidosis. The association of brucellosis and secondary amyloidosis has not been documented in literature till date. However, like tuberculosis and osteomyelitis, brucellosis is a chronic infection and can cause AA amyloidosis. Nevertheless, recurrent renal cyst infections as a cause of amyloidosis cannot be excluded in this case.

CONCLUSION

Hepatic brucelloma is a rare manifestation of chronic *Brucella* infection and closely mimics the neoplastic masses of the liver. A high index of suspicion should be kept in persons with occupational exposure and from endemic regions and needs to be excluded by serological and culture studies. The development of AA amyloidosis in the present case may be ascribed to chronic brucellosis; however, chronic renal cyst infections of ADPKD cannot be excluded.

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The patient's family members signed the consent declaration authorizing data publication, and the manuscript has been approved by the Research Ethical Committee of the institution.

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Correspondence

Kirti Gupta

Postgraduate Institute of Medical Education and Research - Department of Histopathology

Sector 12 – Chandigarh – India

Phone: +91-172-2755105

kirtigupta10@yahoo.co.in