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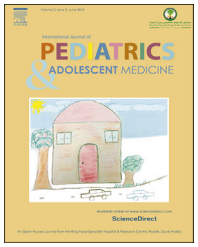

INSTRUCTIVE CASE

Fever of unknown origin and liver mass in a Saudi child

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KEYWORDS
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Fever of unkown origin

Abstract Inflammatory pseudo tumor (IPT) is a rare benign lesion that can occur in any organ in the body. IPT is histologically characterized by the presence of inflammatory cells, especially, plasma cells, spindle-shaped cells, and myofibroblasts.

Many cases of IPTs affecting multiple organs in both adults and children have been documented in the literature. Fifty-five cases of hepatic IPTs have been reported in children, and all of them were managed by surgical resection. Limited data are available on IPTs in Arabs.

Our aim was to report the case of an 8-year-old Saudi boy who was referred to our hospital with fever of unknown origin since 3 months with associated weight loss and a hepatic mass, and was found to have an IPT of the liver, which was confirmed after surgical resection.

8 years old Saudi boy who presented with fever and liver mass. Ultrasound and MRI abdomen showed heterogeneous liver mass. After surgical resection, his mass histology going with inflammatory pseudo tumor. Following surgical resection his fever subsided.

The findings of the present case report show that fever and liver mass in children can be manifestations of a rare disease such as IPT, which should be considered in the differential diagnosis when all investigations are inconclusive. Based on the literature review, surgical excision seems to be the best treatment strategy for this condition. However, the imaging findings, especially the size and location of the mass, must be carefully discussed with the surgical team before the operation.

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1. Introduction

Inflammatory pseudo tumor (IPT) is a rare benign lesion that can occur in any organ in the body [1]. IPT is histologically characterized by the presence of inflammatory cells, especially, plasma cells, spindle-shaped cells, and myofibroblasts. The exact etiology is unknown, but in some cases, IPT has arisen after trauma, infection, immune-autoimmune condition, low grade fibro sarcoma with inflammatory surgery or the removal of a malignancy, e.g., Wilms tumor [2,3]. Although IPT is a rare benign tumor, cases of IPT recurrence and metastasis have been reported. In addition, this tumor can cause symptoms such as biliary obstruction, portal hypertension, vascular thrombosis, cirrhosis, and hepatic failure. IPT most commonly involving the lung and orbit, but it can affect any organ, including the liver, spleen and lymph nodes. The diagnosis is difficult owing to the nonspecific clinical, laboratory and imaging features [4].

Many cases of IPTs affecting multiple organs in both adults and children have been documented in the literature. Fifty-five cases of hepatic IPTs have been reported in children [4,5], and all of them were managed by surgical resection. Limited data are available on IPTs in Arabs. In Saudi Arabia, a few cases have been reported of IPTs in adults, involving the orbit and lungs, and occurring following hip replacement surgery with metal-on-metal implants [6,7]. To our knowledge, no cases of hepatic IPTs in Saudi children have been documented.

Our aim was to report the case of an 8-year-old Saudi boy who was referred to our hospital with fever of unknown origin since 3 months with associated weight loss and a hepatic mass. He was found to have an IPT of the liver which was found after surgical resection.

2. History and physical examination

An 8-year-old Saudi boy who was previously healthy presented to a local Saudi hospital in June 2014 with right hip joint pain and difficulty in walking. Hip joint aspiration was performed, and the results were inconclusive. He was treated for septic arthritis with a full course of intravenous antibiotics. His condition improved with this treatment, and he was then sent home. A few days after discharge, he started to have daily spikes of fever, which reached 39 °C and only partially responded to antipyretics. He had no other clinical symptoms at this time. He was again admitted to a local hospital for 6 weeks. A physical examination revealed a palpable, tender liver, 4–5 cm below the costal margin, with no other abnormal findings. During his hospital stay, several laboratory investigations were performed to rule out infectious and inflammatory conditions, but all of them yielded inconclusive results. He was empirically treated with antibiotics, without any change in the fever spikes. Radiological studies, including chest x-ray, were normal. An ultrasound examination revealed a nonhomogenous liver mass measuring 4 × 4 cm, which was possibly a solid or vascular tumor. The child was then referred to King Faisal Specialist Hospital and Research Centre, Riyadh for further evaluation and management.

Upon admission, he continued to be febrile (range, 38°C–39 °C) with no specific pattern of fever. His appetite was poor, and he was losing weight. A clinical examination showed that the child was pale and had tenderness in the upper right quadrant of the abdomen. No other abnormal findings were detected.

3. Laboratory investigations

Laboratory investigations showed leukocytosis with microcytic hypochromic anemia. Raised levels of inflammatory markers (C-reactive protein, 170–240 mg/l; erythrocyte sedimentation rate, 106–140 mm/h). Liver enzymes and bilirubin levels were mildly elevated (alanine transaminase, 40–58 U/l; alkaline phosphatase, 129–250 U/l; aspartate transaminase, 50–144 U/l; gamma-glutamyl transpeptidase, 50–70 U/l; total bilirubin, 45–70 μmol/l; and direct bilirubin, 15 μmol/l). Coagulation profiles showed persistently high international normalized ratio (1.3–1.9 HI), prothrombin time (PT; 18–21 s), partial thromboplastin time (PTT; 40–58 s), factor VIII (>2 IU/ml), factor IX (1.17 IU/ml) and D-dimer levels (110–165 μg/l), and coagulation level was not corrected after mixing study (PT, 16 s; PTT, 50 s). Tests for infections also yielded negative results; the work-up for infections included blood culture, fungi tell (fungitell), fungal cultures, tests for ova and parasites, tuberculosis skin test, quantiFERON TB test. Serologic tests for hepatitis A, B and C, schist soma (Shistosoma) antibody titers, malarial serology, Q fever serology, *Echinococcus* antibody titers, *Brucella* antibody titers, Epstein–Barr virus serology, cytomegalovirus antibodies, human immunodeficiency virus antibodies and amoeba antibodies. Immunological work-up, to rule out chronic granulomatous disease, hyper IgE and lymphocyte adhesion defect and hemophagocytic syndrome, was negative. Inflammatory disease work-up included tests for antinuclear, anti-cardiolipin and anti-phospholipid antibodies, all of which were negative. Tumor markers, including alpha-fetoprotein, CA 19-9, CA 15-3, CA 12-5, carcinoembryonic antigen and procalcitonin, were tested for to rule out malignancy; all of these tests produced normal results.

4. Radiological investigations

Radiological investigation was repeated to assess the tumor size and confirm the primary findings. Ultrasonography of the abdomen showed a well-defined, heterogenic mass, measuring 4 × 6 cm, in the right upper quadrant with complete thrombosis of the right hepatic vein (Fig. 1). The initial impression was a vascular tumor or malignancy. For this reason, magnetic resonance imaging was performed, and it showed a heterogeneous solitary lesion in the right hepatic lobe with nonspecific radiological appearance (Fig. 2).

Our patient underwent multiple ultrasound-guided core and fine needle liver biopsies. The liver mass located in the right lobe was aspirated using a 25-gauge needle and stained with Diff-Quik stain. The aspirate showed a small amount of cellular yield with benign liver cells mixed with benign-looking histiocytes (Fig. 3A and B). The recommendation was to perform a Tru-Cut needle biopsy for the appropriate staining and immunohistochemical studies. The Tru-Cut needle biopsy was obtained under imaging guidance and tissues were sent for appropriate staining and

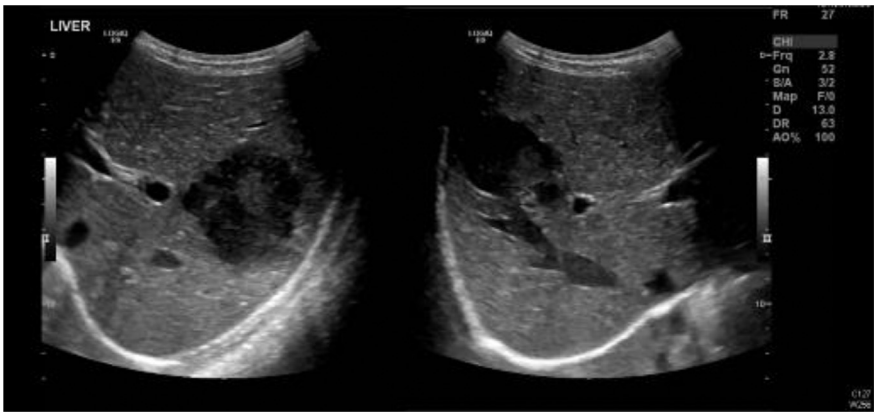

Figure 1 Ultrasound examination of the upper abdomen showing a heterogeneous mass, measuring 4 × 6 cm, in the right hepatic lobe.

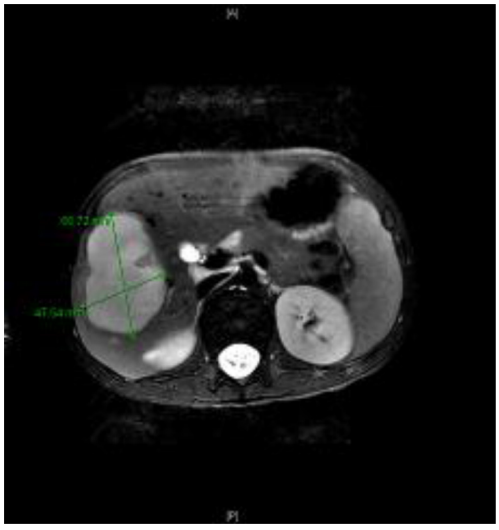

Figure 2 T2-weighted MRI of the abdomen showing a solitary, moderate-sized, complex mass occupying the right lobe of the liver. The differential diagnosis included liver malignancy with extension to the right hepatic vein.

immunohistochemical studies; the results showed a mixture of chronic inflammatory cells and sheets of histiocytes with abundant cytoplasm. Acid-fast bacilli and fungal infection were excluded by special stains. The biopsy showed no obvious pathological or immunohistochemical features of inflammatory myofibroblastic tumor (negative smooth muscle actin and activin receptor-like kinase 1). The other differential diagnosis was dendritic sarcoma, but the biopsy specimen was negative for both CD21 and CD23. Inflammatory bowel disease was also raised as a possible diagnosis, and so, an endoscopic intestinal biopsy was performed, but the findings were negative.

After a multidisciplinary team meeting and discussion with a liver pathologist, the decision was made to perform an excisional biopsy to obtain a better tissue sample for diagnosis. Because of the size and location of the mass, the excisional biopsy was performed by a liver transplant surgeon in August 2014. Under general anesthesia, an L-shaped incision was made in the right subcostal region with an upper midline extension, and a Hampson—Farley self-retaining abdominal retractor was used to enter the abdomen via this incision. Then, exploration of the abdomen was performed, and no tumor extension or metastasis was found in the omentum or peritoneum. The lesion was confined to the right lobe of the liver, as previously seen on the imaging studies, and had a diameter of approximately 5 cm. Therefore, transection of the hepatic parenchyma of the right lobe of the liver, followed by removal of the right hepatic lobe was performed. After the removal of the mass, fever subsided, and antibiotic therapy was stopped after completing the postoperative course. The postoperative laboratory investigation, including complete blood count, tests for inflammatory markers and coagulation profile, showed normal findings. The patient was then sent home, and regularly followed up by the hepatology and liver transplant teams.

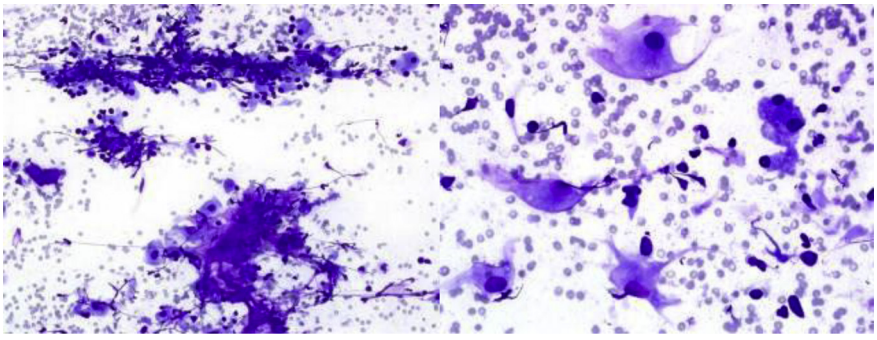

Figure 3 **A and B**. Smears containing a mixture of benign hepatocytes and histiocytes (Diff-Quik stain, ×40).

Figure 4 Cross-section of the mass is well demarcated and has a white—yellow, fleshy cut surface.

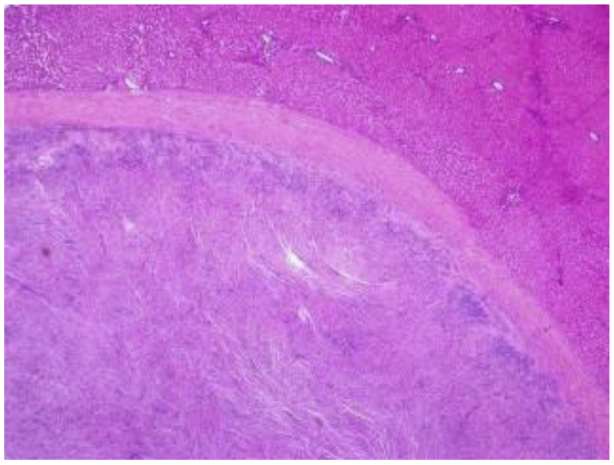

Figure 5 The mass is separated from the surrounding tissue by a thick fibrous capsule.

5. Pathological findings

The resected right lobe of the liver showed two lesions separated by 1.5 cm. The largest mass measured 8 × 6 × 5 cm, and had a white fleshy cut surface. The mass was surrounded by a well-demarcated thin capsule (Figs. 4 and 5). Microscopic examination showed similar morphology to that of the needle biopsy specimen, with a mixture of inflammatory cells and sheets of histiocytic. The inflammatory cells mainly consisted of plasma cells and mature lymphocytes, and were largely concentrated in the sub capsular area and around the blood vessels (Figs. 6 and 7A, B). No granuloma or necrosis was seen. All special stains and immunohistochemical studies were repeated on the resected nodule, with mostly negative results. The histiocytic were positive for the histiocytic marker CD68 (Fig. 7A and B). The plasma cell infiltrate was stained for IgG4, but the number of positively stained cells was insufficient for a diagnosis of IgG4-related disease (Fig. 8).

6. Discussion

A review of the literature revealed a few reports of IPTs in patients belonging to different age groups. In most of the reported cases, surgical resection was required to treat the symptoms [1]. The recurrence rates of IPT are 3%—10% in adults and 14% in children [8]. The risk factors for IPT recurrence are irregularity of tumor margins, failure to resect the whole tumor and extension beyond the involved organ or the involvement of many organs [8]. Hepatic tumors are rare, affecting men more than women. They mostly present with fever and abdominal pain. In literature, review most of the cases are treated by resection [9].

In our patient, fever was completely resolved following tumor resection. The inflammatory marker levels returned to normal in a couple of months, and the patient was followed up by the liver transplant and hepatology teams.

Before the right hepatic lobectomy, the hepatology team recommended a liver biopsy of the normal liver tissue to rule out any systemic illness that could have caused recurrence. This precaution was very important in our patient, given the large size of the tissue to be removed. The patient may require a liver transplant in the future, if systemic disease had been present. The tumor was large, measuring around 5 × 5 cm, occupying most of the right hepatic lobe and causing vascular compression. This is why the best treatment option was resection.

Our patient had a prolonged PT (range and unit) and elevated factor VIII level (range and unit), which were most likely a result of liver dysfunction. Liver biopsy is an invasive procedure that can be complicated with life-threatening bleeding [10], which was a distinct possibility in our patient. Therefore, we administered fresh frozen plasma and factor VII prior to the biopsy and total excision of the mass.

Factor VII can be used as an exogenous source to augment the coagulation cascade [11]. There are limited data on the use of factor VII in liver disease-related coagulation dysfunction, and many doses have been reported in the literature. In one study, four different doses (5, 20, 80, and 120 μg/kg) were used in patients with liver cirrhosis prior to laparoscopic liver biopsy, and transient normalization of PT was achieved in all four groups [12]. There was no difference in the amount of hepatic bleeding after the procedure in the four groups, and only two patients developed complications (disseminated intravascular coagulation in one patient and portal vein thrombosis in the other). The authors mentioned that these complications were not directly related to the use of factor VII [13]. We recommend that patients with hepatic vein thrombosis who require major surgery should not be administered high doses of recombinant activated factor VII, as this can induce further thrombosis (14).

The findings of the present case report show that fever and liver mass in children can be manifestations of a rare disease such as IPT, which should be considered in the differential diagnosis when all investigations are inconclusive. Based on the literature review, surgical excision seems to be the best treatment strategy for this condition. However, the imaging findings, especially the size and location of the mass, must be carefully discussed with the surgical team before the operation. Further studies are required to determine the safest dose of recombinant activated factor FVII in patients with liver disease-related coagulopathy.

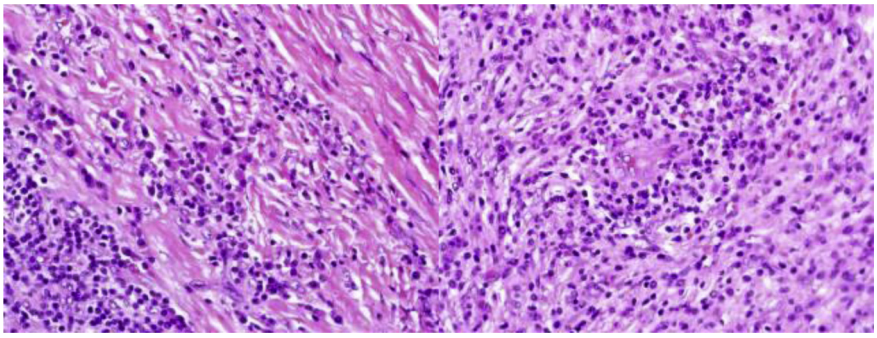

Figure 6 **A and B**. Lymphoplasmocytic cell infiltration is concentrated in the subcapscular area and around the blood vessels (hematoxylin and eosin, ×40).

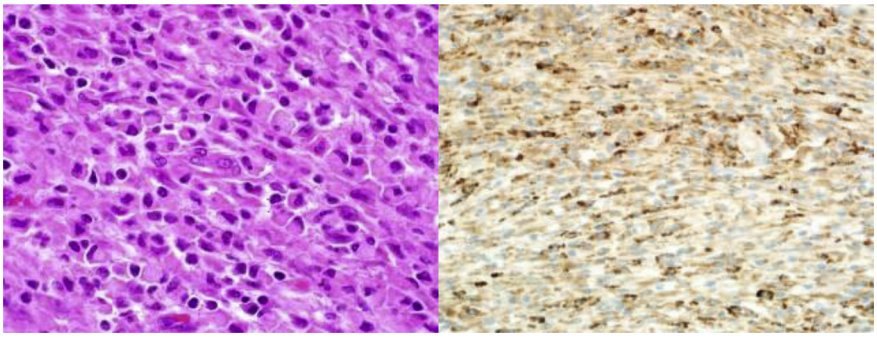

Figure 7 **A and B**. All the histiocytes in the tissue specimen are positive for CD68 (hematoxylin and eosin, CD68; ×40).

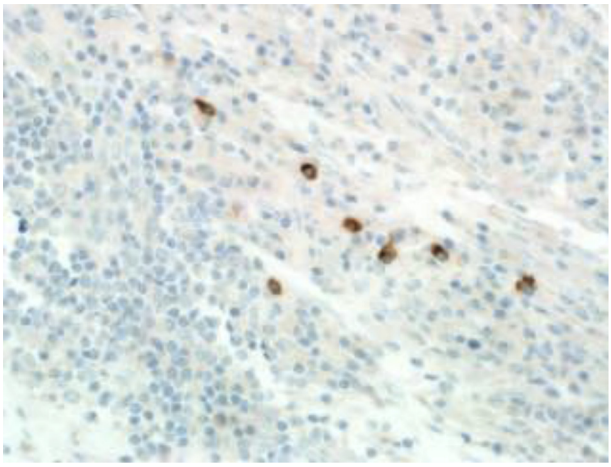

Figure 8 A few plasma cells are positive for IgG4 (IgG4, ×40).

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