INSTRUCTIVE CASE

Fever of unknown origin and liver mass in a Saudi child

Fawzah Alrwuili*

King Faisal specialist Hospital and Research Centre Riyadh, Pediatric Department, Saudi Arabia

Received 13 May 2015; received in revised form 21 May 2015; accepted 26 May 2015
Available online 2 July 2015

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.

Copyright © 2015, King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

* Tel.: +966 114647272x27763.
E-mail address: falrowaily@kfshrc.edu.sa.
Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

http://dx.doi.org/10.1016/j.ijpam.2015.06.002
2352-6467/2015, King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 non-specific 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 implants [6,7]. To our knowledge, no cases of hepatic IPTs in Saudi children have been documented.

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 recommended treatment 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 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 NI), 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, fungal 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 non-specific radiological appearance (Fig. 2).
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 1](image1.png) Ultrasound examination of the upper abdomen showing a heterogeneous mass, measuring 4 × 6 cm, in the right hepatic lobe.

![Figure 2](image2.png) 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.

![Figure 3](image3.png) A and B. Smears containing a mixture of benign hepatocytes and histiocytes (Diff-Quik stain, ×40).
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.
References

[1] Masato S, Hitoshi I, Norio S, Atsushi T, Minoru K, Junko H. Inflammatory pseudo tumor of the liver: case report and review of the literature. J Pediatr Surg 2001;36(4):663–6.

[2] Vujanic GM, Millvanovic D, Aleksandrović S. Aggressive inflammatory pseudo tumor of the abdomen 9 years after therapy for Wilms tumor. Cancer 1992;70:2362–6.

[3] Newbould MJ, Kelsy A, lendon M, Gururangan S. Inflammatory pseudo tumor of the liver masquerading as metastasis in child treated for nephroblastoma. Med Pediatr Oncol 1992;20: 172–5.

[4] Horiuchi R, Uchida T, Kojima T, Shikata T. Inflammatory pseudo tumor of the liver: clinic pathologic study and review of the literature. Cancer 1990;65:1583–90.

[5] Shek TWH, Ng IOL, Chan KW. Inflammatory pseudo tumor of the liver: report of four cases and review of literature. J Surg Pathol 1993;17:231–8. Cancer 77:778–784, 1996.

[6] Suliman AA, Nelson VG, Masri BA, Duncan CP, Garbuz DS. The natural history of inflammatory pseudo tumor in asymptomatic patients after metal-on-metal hip arthroplasty. Clin Orthop Clin Res 2013;47(12):3814–21.

[7] Hajjar WA, Ashour MH, Al-Rikabi AC. End bronchial inflammatory pseudo tumor of the lungs. Saudi Med J 2001;22(4):366–8.

[8] Chan YF, White J, Brash H. Metachronous pulmonary and cerebral inflammatory pseudo tumor in a child. Pediatr Pathol 1994;14:805–15.

[9] patnana Madhavi, Sevrukov AB, Elsayes KM, Viswanathan C, Lubner M, Menias CO. Inflammatory pseudotumor: the Great Mimicker. Am J Roentgenol 2012;198:W217–27.

[10] Grant A, Neuburger J. Guidelines for the use of liver biopsy in clinical practice. Gut 1999;45(Suppl. IV):IV11.

[11] Veldman A, Hoffman M, Ehrenforth S. New insight in to the coagulation system and implication for new therapeutic options with recombinant factor via. Curr Med Chem 2003;10: 797–811.

[12] Bernstein DE, Jeffers L, Erhardtse E, Reddy KR, Glazer S, Squiban P, et al. Recombinant factor Vila corrects prothrombin time in cirrhotic patients: a preliminary study. Gastroenterology 1997;113:1930–7.

[13] Fuat HS, Robert KG, Hikmet A, Ali C, Klaus G. Delicate balance of bleeding and thrombosis in end stage liver disease and liver transplantation. Digestion 2013;88:135–44.