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Unlucky versus coincidence: Dual hepato-pancreatico biliary diagnoses in a six-year-old

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ABSTRACT

We describe a case of inflammatory myofibroblastic tumor presenting as a head of pancreas mass in a six-year-old girl. The etiology of such lesions is elusive, with a poorly understood malignant potential. One hypothesis is that they occur in areas of inflammation and trauma. The tumor occurred two years after this same patient had a Type I choledochal cyst excised with Roux-En-Y hepaticojejunostomy.

Inflammatory myofibroblastic tumors (IMTs) have undergone many nomenclature changes in recent years, reflecting incomplete understanding of their etiology, pathogenesis and clinical behavior [1]. Also known as inflammatory pseudotumors or plasma cell granulomas, they are rare neoplasms [1], and rarer still in children. This report presents a child who developed an IMT in a post-operative field.

1. Case report

A 6-year-old female presented with a one-month history of fatigue, vomiting, anorexia, early satiety and weight loss. She had no abdominal pain and physical examination was unremarkable with neither jaundice nor a palpable abdominal mass being noted.

Ultrasound investigation revealed a right hypochondrial mass. A portal venous contrast computed tomography (CT) study of the abdomen showed a 6 × 6.2 cm mass arising from the head of pancreas, with atrophy of the pancreatic body and tail. No biliary or pancreatic ductal dilatation was noted and there were no other lesions (Fig. 1). Blood tests showed a microcytic anemia with normal inflammatory markers, normal hepatic and renal function, a lipase of 79 U/L (normal value < 60 U/L), and a normal ferritin.

Two years previously, a Type I choledochal cyst had been diagnosed in this patient after she presented with obstructive jaundice. She underwent an uncomplicated choledochocystectomy with Roux-En-Y hepaticojejunostomy. Pathological examination of the resected specimen demonstrated a choledochal cyst with chronic inflammation and fibrosis. She made a full recovery, and 6 monthly post-operative ultrasound scans were normal prior to her symptomatic presentation.

An endoscopic retrograde cholangiopancreatogram (ERCP) was organized to obtain a tissue diagnosis. Examination of the biopsy specimens taken showed a stromal lesion of intermediate biological behavior, favoring an IMT. The biopsies were positive for anaplastic lymphoma kinase (ALK), B-cell lymphoma 2 (BCL2) and Cyclin D1; human herpesvirus 8 (HHV8) was negative.

Following multidisciplinary consultation, crizotinib (Pfizer, New York City, USA), an ALK and ROS1 inhibitor, was prescribed prior to planned resection. Shrinkage of the tumor to 2.8 × 2.4 cm over 4 months was observed. The patient went on to have a pancreaticoduodenectomy (Fig. 2) with posterior pancreaticogastrostomy and anterior gastrojejunostomy (Fig. 3). The previous hepaticojejunostomy was left undisturbed. Histological margins were tumor free. She made a speedy recovery but was readmitted a short time later with delayed gastric emptying which resolved with parental nutrition support and gut rest. She remains well nine months later, with no evidence of recurrence.

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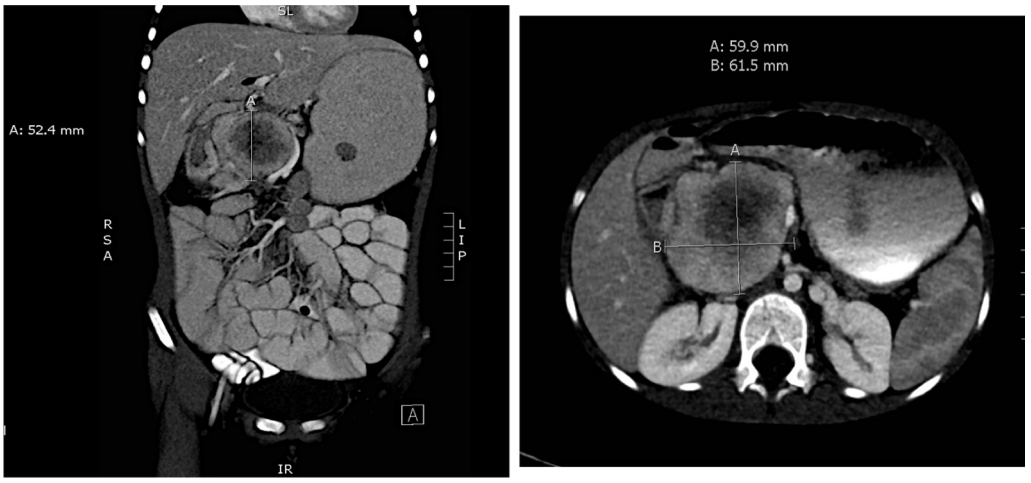

Fig. 1. Coronal and axial computed tomography images demonstrating the head of pancreas mass measuring approximately 6 × 6 cm.

2. Discussion

IMTs are rare, solid lesions occurring most commonly in the bronchial tree, retroperitoneum and abdominal cavity [2]. When examined histologically, they are composed of fibroblast and myofibroblast infiltrates with a background chronic inflammatory infiltrate of eosinophils, plasma cells and lymphocytes. Although they clinically and radiologically mimic neoplasms, IMTs have questionable potential for aggressive behavior. Recognition of ALK gene rearrangement and cytogenetic aberrations support the concept of IMTs being a neoplastic lesion and as such the World Health Organisation classifies them as a distinctive neoplasm with intermediate biological behavior [2]. Complete surgical excision appears to be curative although cases of metastatic disease have been reported [3]. Evidence suggests that pathological features of atypia, p53 expression and aneuploidy may predict IMTs with more aggressive potential [4].

Several biological markers have been identified as having diagnostic and therapeutic importance, although these are not specific for IMTs. Anaplastic lymphoma kinase (ALK) rearrangements on chromosome 2p23 result in aberrant ALK expression in 40–50% of IMTs [5,6]. Children and young adults diagnosed with IMTs appear more likely than adults over the age of 40 to harbor ALK rearrangements in the myofibroblastic component of the tumor; the inflammatory component does not exhibit this change. ALK inhibitors such as crizotinib are therefore potentially of benefit.

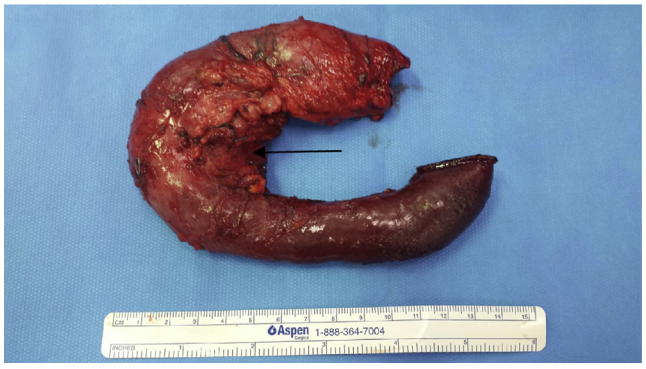

Fig. 2. Pancreaticoduodenectomy specimen. Arrow points to area of IMT which had a rubbery consistency.

Given the location of our patient's disease and the desire to perform a less extensive, albeit complete, resection, neo-adjuvant treatment was used with the intention of shrinking the lesion. IMT response to crizotinib has been described. Butrynski et al. [6] reported a partial response to crizotinib in a 44-year-old man with diffuse intraabdominal IMT harboring ALK rearrangement detected by fluorescent in situ hybridisation (FISH). Following surgical debulking, the initial substantial response to therapy lasted 6 months, after which the tumor began to re-grow. After further surgical debulking of the recurrent tumor, the patient remains on long-term crizotinib with no radiological evidence of recurrence. The second patient in Butrynski's report was a 21-year-old male with a gastric IMT. The resected specimen was negative for ALT rearrangement and when recurrent disease was detected five months later, crizotinib was initiated and re-staging showed worsening of disease with no response to therapy. The authors concluded that there was potential for long-term response in favorable tumor cell populations to crizotinib; this formed the rationale for administration of the drug to the patient described in our paper. Her response gives further support to Butrynski's findings. Further, targeted ALK therapy in pediatric malignancies was found to be safe in a Phase 1 trial in patients aged 12 months to 22 years [7]. Anti-tumor activity was enriched in patients with known ALK rearrangements and the drug was well tolerated. Phase 2 of this US trial is due for completion in 2017 [8].

The etiology of IMTs has remained elusive since they were first described in 1939 [9]. Neoplastic, infectious, autoimmune and genetic etiologies have all been proposed. Identification of human herpesvirus 8 (HHV-8) and Epstein–Barr virus (EBV) DNA sequences in IMT specimens was initially promising [10,11] although this has not been substantiated in pediatric case series [3,12]. Human interleukin 6 (IL-6) and cyclin D1 overexpression have been reported in a case series of 7 patients [13], and p53 modulated alterations have been implicated in those IMTs harboring malignant transformation [2].

Accurate demographic data regarding anatomical sites affected by IMTs are difficult to obtain given the interchangeable terms historically used to describe these lesions. Janik et al. [14] collated 274 pediatric cases of IMTs reported in the literature: this is perhaps the largest summative series. One third of IMTs occurred in the pulmonary tree. Intra-abdominal IMTs made up the majority of extrapulmonary locations with the omentum, retroperitoneum and mesentery being the most common. IMTs have a predilection for patients in the first two decades of life, with the youngest published