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MINIREVIEWS

Inflammatory myofibroblastic tumor of the distal common bile duct: Literature review with focus on pathological examination

Fleur Cordier, Anne Hoorens, Liesbeth Ferdinande, Jo Van Dorpe, David Creytens

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Abstract

Inflammatory myofibroblastic tumor (IMT) of the biliary tract is rare, and often difficult to diagnose or to distinguish from other tumors due to its atypical clinical presentation and nonspecific radiological features. Histologically, IMTs are (myo)fibroblastic neoplasms with a prominent inflammatory infiltrate. They are characterized by receptor tyrosine kinase gene rearrangements, most often involving an anaplastic lymphoma kinase (*ALK*) translocation. The final diagnosis of IMT depends on histopathology and immunohistochemical examination. In this manuscript, we provide a clinical and morphomolecular overview of IMT and the difficulties that may arise in using immunohistochemical and molecular techniques in diagnosing IMT.

Key Words: Inflammatory myofibroblastic tumor; Fluorescence in situ hybridization; Next-generation sequencing; Mesenchymal tumors of the gastrointestinal tract

Core Tip: Inflammatory myofibroblastic tumor (IMT) of the intrapancreatic biliary tract is rare and often difficult to diagnose. In this manuscript, we give a recent update of the clinicopathological features of IMT with focus on the pathological and molecular characteristics.

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INTRODUCTION

Inflammatory myofibroblastic tumor (IMT) is a (myo)fibroblastic neoplasm with a prominent inflammatory infiltrate, consisting mainly of lymphocytes and plasma cells. Originally, IMT was reported in the lung by Brunn[1] but the term IMT was first proposed in 1990 by Pettinato *et al*[2]. It was regarded as an inflammatory pseudotumor until it was officially considered a separate entity by the World Health Organization (WHO) in 2002[3-5]. In the gastrointestinal tract, IMT occurs mainly in the small intestine and colon. It typically forms in the submucosa, muscularis propria or mesentery and gives rise to abdominal pain, intestinal obstruction or fever. IMT of the pancreas and biliary tract is extremely rare; few cases have been reported[4-7].

Recently, we encountered an IMT in the lumen of the distal common bile duct near the ampulla, in a 64-year-old woman. This lesion was discovered incidentally during follow-up imaging of the patient's metastatic breast carcinoma. Radiological examination revealed a mass, measuring approximately 17 by 14 mm, exerting pressure on the distal choledochus and resulting in bile duct dilatation of 11 mm. Interestingly, the patient did not exhibit any symptomatic signs related to this finding (no signs of obstructive jaundice). Clinically, there was suspicion of an ampullary carcinoma, leading to the decision to perform a Whipple resection. Macroscopically, a myxoid lesion was seen intrapancreatic, occupying the lumen of the common bile duct (2.1 cm × 1.6 cm) (Figure 1). Microscopical examination revealed an intraluminal mesenchymal lesion consisting of plump spindle cells with pale cytoplasm containing a vesicular nucleus. The stroma was myxoid with an inflammatory infiltrate composed of lymphocytes, plasma cells, macrophages and scarce eosinophils (Figure 2A). There was no necrosis or brisk mitotic activity. On immunohistochemistry (IHC), the tumor was negative for desmin, SOX10, S100, pancytokeratin AE1/AE3, DOG1 and CD34. IgG4/IgG ratio was normal. There was cytoplasmic immunohistochemical positivity for anaplastic lymphoma kinase (ALK) (Figure 2B), rendering the diagnosis of an IMT.

In this case, the histopathological differential diagnosis included gastrointestinal stromal tumor (GIST) and IgG4-related disease, which were ruled out by IHC. However, due to the exceptionally rare location of the lesion in the lumen of the common bile duct, additional fluorescence in situ hybridization (FISH) was performed to confirm the diagnosis of an IMT. Unfortunately, FISH could not confirm an ALK rearrangement, with only a split of signals in 12% of the counted tumor cells (equivocal result). Subsequently, RNA next-generation sequencing (NGS) was performed and detected an *EML4::ALK* fusion, confirming the diagnosis of IMT in our patient[8].

CLINICAL MANIFESTATIONS

The age group for IMT is wide, but it usually occurs in children and young adults with no sex predilection[3-5,9,10]. In the pancreas, IMT usually occurs in the head of the pancreas and in the bile duct, it is more commonly seen in the hilus of the liver. It causes painless obstructive jaundice, abdominal pain, weight loss and fever[4,6,9-11].

Because of the rarity of IMT in the common bile duct or pancreatic head, its atypical clinical presentation and nonspecific radiological features, it is often difficult to distinguish IMT from other tumors. Therefore, most IMTs are surgically removed before definitive diagnosis[3-5,9,10].

PATHOLOGICAL AND MOLECULAR FEATURES

IMTs may be solid, fleshy or gelatinous, with a white to yellowish-brown cut surface. In a minority of cases calcifications, bleeding and necrosis occur. The tumor size ranges from 1 cm to 20 cm, with an average of 6 cm[12-14].

Histologically, IMTs are composed of myofibroblastic spindle cells and inflammatory cells. Coffin *et al*[15] described three basic histological patterns: A myxoid/vascular pattern, a compact spindle cell pattern and a hypocellular fibrous (fibromatosis-like) pattern. These patterns are often seen in combination within the same tumor. The myxoid/vascular pattern has a fasciitis-like appearance, with loosely arranged plump spindle cells in an edematous or myxoid stroma and a prominent vasculature. The inflammatory infiltrate often demonstrates more neutrophils and eosinophils, and less plasma cells than in the other two patterns. The compact spindle cell pattern resembles fibrous histiocytoma with compact spindle cells intermixed by inflammatory cells (lymphocytes, plasma cells and eosinophils). The fibromatosis-like pattern is relatively hypocellular with a dense collagenous stroma showing scattered lymphocytes, plasma cells and eosinophils resembling a desmoid fibromatosis or scar[12,13,16].

The spindle cells of IMT are typically uniform and predominantly myofibroblastic. Mild nuclear pleomorphism may be seen, but hyperchromasia is absent[5,13]. About half of the cases contain scattered 'ganglion-like' cells. These are larger polygonal cells with abundant amphophilic to eosinophilic cytoplasm, large vesicular nuclei and prominent nucleoli, similar to those seen in proliferative fasciitis[12,14]. Mitotic activity is low (0–2 mitoses per 10 high power fields, and atypical mitoses are rare[5,12,13,15,17]. Necrosis and vascular invasion are rare, but can be observed[5,12,13,15,18]. Coffin *et al*[15] showed that the presence of necrosis, hypercellularity and ganglion-like cells was not related to clinical features, outcome or ALK reactivity. The presence of atypical mitoses should raise the possibility of an alternative diagnosis. In rare cases, IMT shows a higher-grade morphology with increased cellularity, epithelioid/histiocytoid or round cell morphology, marked nuclear atypia, frequent mitoses, atypical mitotic figures and/or necrosis[5,12,13,15,16,19-21]. This variant is referred to as epithelioid inflammatory myofibroblastic sarcoma (EIMS). EIMS occurs mainly intra-abdominal, is associated with a more aggressive course and shows a male predominance[5,7,16,19,22].

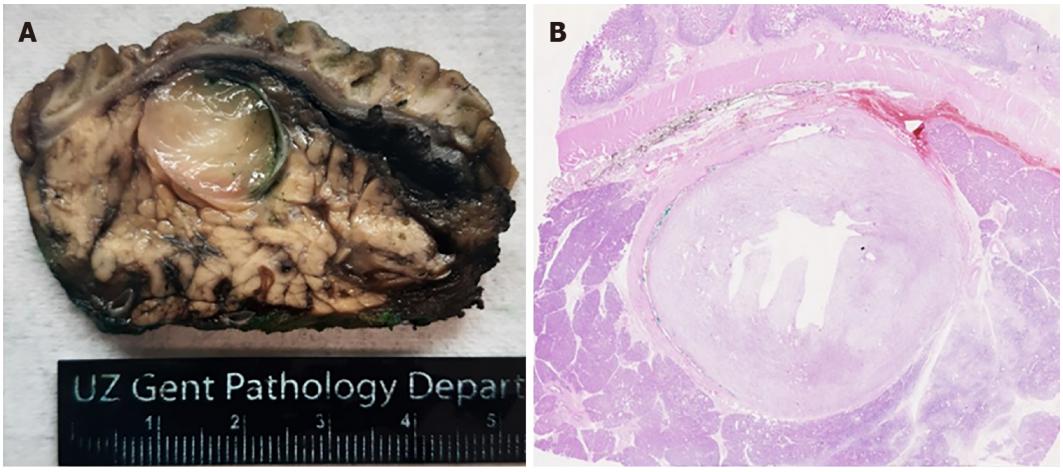

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Figure 1 Inflammatory myofibroblastic tumor of the common bile duct. A: Macroscopic picture showing a gelatinous lesion in the lumen of the intrapancreatic part of the common bile duct; B: Microscopic examination of the same lesion confirming its myxoid nature (hematoxylin and eosin, original magnification 10x).

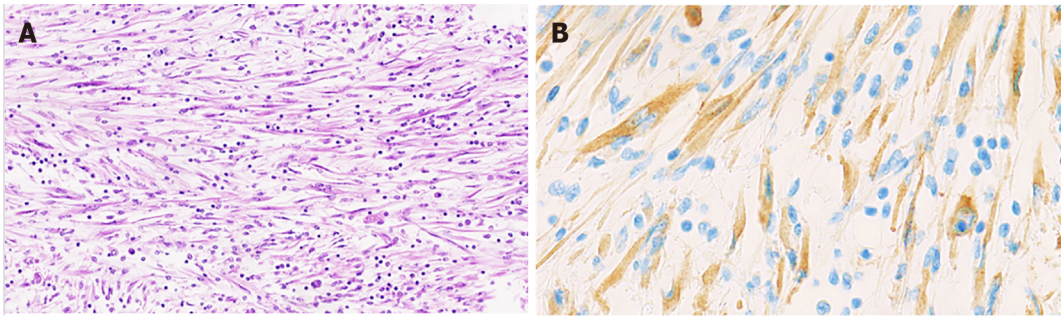

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Figure 2 Histological and immunohistochemical characteristics. A: At high magnification this inflammatory myofibroblastic tumor is composed of plump spindle cells with a vesicular nucleus and pale cytoplasm. The stroma is myxoid with an inflammatory infiltrate composed of lymphocytes, plasma cells, macrophages and scarce eosinophils (hematoxylin and eosin, original magnification, 100x); B: The lesion demonstrates obvious ALK positivity in the spindle cells (original magnification 500x).

Immunohistochemically, IMTs demonstrate diffuse positivity for vimentin, muscle-specific actin and smooth muscle actin; and may show focal reactivity for cytokeratin, clearly showing the myofibroblastic nature of the tumor[5,13,15]. Staining for desmin and calponin is often focal[7,12,13,18]. A significant proportion of IMTs show nuclear MDM2 expression[12,15,18].

IMTs are characterized by the presence of receptor tyrosine kinase gene rearrangements. This finding provides further support for the neoplastic nature of IMTs and their differentiation from inflammatory pseudotumors[5,8,12,23,25]. About 50% of IMTs, particularly those arising in young patients, show chromosomal translocations involving the *ALK* locus on chromosome 2p23, leading to activation of the ALK tyrosine kinase, resulting in ALK protein expression on IHC[5,8,12,19,23,24,26]. Multiple fusion partners to *ALK* have been described in IMTs, including *TPM3*, *TPM4*, *CARS*, *ATIC*, *SEC31L1*, *CLTC,* among others[5,8,23,25,27-32]. *EML4::ALK* gene fusions, as present in our case, have been described in IMTs, mostly occurrng in the lung and soft tissue[8]. ALK overexpression can be detected on IHC, however localization within the cells seems to be determined by the fusion partner. In general, a diffuse cytoplasmatic staining is seen due to the cytoplasmatic localization of the fusion partner of *ALK, e.g. TPM3*, *TPM4*, *CARS*, *ATIC* and *SEC31L1*[12,19,30-32]. A granular cytoplasmic staining has been described in IMTs with *CLTC* as fusion partner, a main structural protein of coated vesicles[12,23,28].

EIMS appear to be characterized by an *ALK::RANBP2* or *RRPB1::ALK* fusion gene transcript[5,12,19,21-23,25]. EIMS with an *ALK::RANBP2* fusion show a nuclear membrane pattern staining for ALK, presumably due to the heteroassociation of the fusion protein with normal RANBP2 at the nuclear pore[12,19,21,23,25]. EIMS with an *RRPB1::ALK* fusion show cytoplasmatic ALK expression with perinuclear accentuation. Lee *et al*[22] suggested, based on the different morphology, molecular fusion transcript and clinical behavior, that EIMS constitutes a distinct subgroup of IMT that is of higher grade, rather than a transformation of conventional IMT. Since these fusion transcripts have not been reported in conventional IMTs, they assume that these specific *ALK* fusions are directly responsible for the high proliferative status and distinctive epithelioid morphology of EIMS[22].

The presence of ALK protein expression, detected by IHC, or *ALK* rearrangement are specific diagnostic markers and are very useful and crucial in the differential diagnosis of IMT. *ALK* gene rearrangements can be detected by FISH. However, equivocal FISH signal counts are occasionally observed. In the study of Yao *et al*[33], IMTs with an equivocal pattern of *ALK* signal count, turned out to be *ALK* fusion-positive by targeted RNA sequencing, suggesting that a low threshold for *ALK* FISH signal counts in IMTs might be proposed, and that more attention should be paid to equivocal (*i.e.* split signals in around 15% of counted tumor cells) *ALK* FISH signal cases. This was also seen in our case with an equivocal signal count (split signals in 12% of counted tumor cells) on FISH, but with a confirmed *ALK* gene fusion by using targeted RNA NGS. In addition, also ALK positivity on IHC should be interpreted with caution due to the possibility of non-rearrangement-induced ALK protein expression, as seen, for example in spindle cell and alveolar rhabdomyosarcoma. In these cases, amplification or upregulation of *ALK* may underly immunohistochemical expression of ALK[34-38]. Further, ALK immunoexpression can be negative in *ALK*-fusion positive IMTs, therefore FISH testing should be performed in IMTs with typical morphologic features, but negative ALK immunostaining[8]. Since only 50% of the IMTs show an *ALK* rearrangement, the absence of ALK on IHC does not exclude the diagnosis of IMT[12]. ALK-negative IMTs are more common in elderly patients and may show more nuclear atypia or atypical mitoses[15]. For tumors resembling IMTs, but that occur in elderly patients and in unusual anatomical locations, or that demonstrate prominent nuclear atypia, more aggressive spindle cell sarcomas should be included in the differential diagnosis *e.g.* myofibroblastic sarcoma, leiomyosarcoma, follicular dendritic cell sarcoma, dedifferentiated liposarcoma, ...[12,39]. In contrast, tumors with typical cytoarchitectural features occurring in the lung or abdomen of paediatric and adolescent patients can be diagnosed as IMTs, even without ALK expression[15].

In addition, *ROS1* rearrangements were identified in a subset of *ALK*-negative IMTs, indicating a new diagnostic marker[8,39]. Antonescu *et al*[8] showed that cytoplasmic ROS1 expression is limited to tumors with *ROS1* rearrangements and that ROS1 IHC is consistently negative in *ALK*-positive IMTs[39]. Also, gene fusions involving *NTRK3, PDGFRB,* and *RET* have been reported[40-42]. *TP53* mutation is an infrequent event in IMT and may not play a major role in its pathogenesis[18].

Since IMT shows an atypical clinical presentation and nonspecific radiological features, the final diagnosis is made on histology. The WHO's 2020 essential diagnostic criteria for IMT in the digestive system are as follows: loose fascicles of plump spindle cells without substantial pleomorphism (except epithelioid type); an inflammatory infiltrate of lymphocytes and plasma cells together with SMA positivity and often combined with ALK or (rarely) ROS1 expression [5].

PROGNOSIS

IMT is a neoplasm of intermediate biologic potential with a tendency for local recurrence and persistent local growth. The risk for distant metastasis is small[5,12,13,15,19]. The most common sites of metastasis are lung and brain, followed by liver and bone. Metastatic disease is usually identified at presentation or within a year of diagnosis[12,43]. Coffin *et al*[15] showed that *ALK* positivity is associated with local recurrence, but not distant metastasis, which was confined to *ALK*-negative lesions. Thus, ALK positivity may be a favorable prognostic indicator in IMT. EIMS is more aggressive and recurs rapidly, with disseminated intra-abdominal disease, variable liver metastases, and a high mortality rate[5,19].

The presence of receptor tyrosine kinase gene rearrangements defines therapeutic targets for IMTs, which may respond to tyrosine kinase inhibitors, such as crizotinib with symptomatic improvement, as well as radiologic response[33,34]. Therefore, it is recommended to perform immunohistochemical staining, FISH or NGS to detect an underlying receptor tyrosine kinase gene rearrangement, especially in recurrent/advanced lesions in which systemic therapy with kinase inhibitors could be beneficial[8].

CONCLUSION

Inflammatory myofibroblastic tumor of the intrapancreatic biliary tract is rare and often difficult to diagnose. In this manuscript, we give a recent update of the clinicopathologic features, focusing on the pathologic and molecular features.

FOOTNOTES

Author contributions: Cordier F performed the writing of the paper and made the figures; Creytens D performed the study concept, design and review of the paper; Hoorens A, Ferdinande L and Van Dorpe J performed review of the paper; all authors read and approved the final paper.

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