

Inflammatory Myofibroblastic Tumor of the Liver and Bile Tract in Pediatric Patients

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Abstract

Inflammatory myofibroblastic tumor is a rare neoplasm of mesenchymal lineage and intermediate malignancy. The most frequent location in the pediatric population is at the level of the abdominal cavity, however liver location and/or bile duct involvement is very rare according to the literature review. This is a pathology with nonspecific symptoms, in the same way it happens with laboratory and radiological analyzes, so the clinical diagnosis is a challenge. The pathological study is essential for the diagnosis and subsequent treatment, in microscopy three characteristic elements can be seen: one made up of cells with a spindle cell appearance, with nuclei with soft characteristics, inconspicuous nucleoli and scant cytoplasm, the second component is the stroma made up of collagen fibers and the third component is the inflammatory infiltrate with a predominance of lymphocytes and plasma cells. These characteristics are difficult to evaluate when biopsy studies and/or freezing techniques are carried out, so we consider it essential to take this pathology into account in the differential diagnosis of neoplasms with the aforementioned characteristics: age and location, since there is a considerable percentage of cases in which the myofibroblastic tumor was misdiagnosed at first. The most frequent genetic characteristic of inflammatory myofibroblastic tumor corresponds to the alteration of the ALK gene, however, alterations in other genes are currently being discovered. It is important that research continues to determine the association between clinical, pathological, and molecular characteristics with prognosis, as well as developing targeted therapies that generate greater benefits in patients.

Keywords: *Mesenchymal Neoplasms; Inflammatory Myofibroblastic Tumor; Little Boy; Hepatic Neoplasms; Bile Duct Neoplasms*

Introduction

The Inflammatory Myofibroblastic Tumor (IMT) according to the World Health Organization is defined as a mesenchymal neoplasm that occurs infrequently and its behavior is of intermediate malignancy, since it can present local infiltration, recurrence and even distant metastasis [1].

The first cases were described in 1954 and were associated with alteration of the ALK gene (called anaplastic lymphoma kinase) [2]. This is an entity that was called an inflammatory pseudotumor [3], however, the definition described by the World Health Organization was later established and several studies began to find associations of the expression of the ALK gene with immunohistochemical studies as well as associated with the prognosis of disease [4,5].

There are no exact figures about the incidence or prevalence worldwide, however various researchers have been reporting the presentation of cases according to age groups, anatomical location and according to each location, so in the United States in one of these Studies have reported an incidence between 150 to 200 new cases annually approximately [6].

Etiology

No etiology has yet been found that is associated with the development of Inflammatory Myofibroblastic Tumor; however there is a genetic alteration that is observed between 50 to 60% of cases, which consists of the alteration of the ALK gene, which is found located on chromosome 2 at the 2p23 locus, this aberration being observed through immunohistochemical studies, which allow us to confirm the diagnosis in paraffin tissue samples [6,7].

Likewise, in recent studies other genetic alterations have been evidenced, which are evidenced less frequently, however it is important to know these because they could influence the prognosis or response to treatment of patients with this pathology, these genes are: ROS 1, PDGFRb, RET and the NRTK [8-11].

Clinical features

This pathology can occur at any age, however it is observed more frequently between the first and second decade of life [12].

Regarding the location, it can compromise various locations, the most frequent being the lung, abdominal cavity, head, neck and mediastinum. In the pediatric population, the most frequent location is in the abdominal cavity, especially at the level of the omentum, mesentery, retroperitoneum, pelvis and more infrequently at intra-abdominal visceral level, liver location and/or bile duct involvement is very rare [12-14].

As mentioned, the hepatic or bile duct localization of Inflammatory Myofibroblastic Tumor is very frequent, however clinical case studies have been reported describing its main clinicopathological characteristics [12-14]. Table 1 shows detail the studies that reported lesions diagnosed as Inflammatory Myofibroblastic Tumor in the liver and bile ducts. Taking into account the most frequent mesenchymal lesions in the liver and bile ducts, the most frequent that have been reported are hemangioma, mesenchymal hamartoma, both are benign lesions, another lesion of intermediate behavior also frequent is hemangioendothelioma, while within the group of the malignant lesions are hepatocellular carcinoma, rhabdomyosarcoma and undifferentiated embryonal sarcoma [15].

Author and Year of publication	Age	Location	ALK	Treatment and Prognosis
Filips A., <i>et al.</i> 2020 [19]	Woman 32 years	Liver: Right lobe	ALK- positive staining, cytoplasmic expression	Treatment: surgical resection Complication: Bilioma Follow-up was carried out for up to 12 months without recurrence.
Prado-Cucho., <i>et al.</i> [20]	Man 7 years	Right hepatic duct with extension to the hepatic parenchyma.	The pattern observed was compact spindle cell and ALK staining was positive at the cytoplasmic level.	Treatment: surgical resection No recurrence was evidenced at 6 years of follow-up.

Thavamani A., <i>et al.</i> 2019. [21]	Woman 10 years	Lesión periportal The myxoid-vascular	ALK staining was negative, actin staining positive	Treatment: Surgical resection, anti-inflammatories and corticosteroids
Watanabe J., <i>et al.</i> 2019 [22]	Woman 70 years	Liver: Right lobe	ALK was not performed, other positive immunohistochemical studies were used for actin, vimentin, among others.	Treatment: surgical resection Follow-up was carried out for up to 7 months without recurrence.
Yamada T., <i>et al.</i> 2017 [23]	Man 50 years	Gall bladder	Positive staining for cytoplasmic ALK and actin.	Treatment: surgical resection The evolution of the patient was not reported.
D’Cunha A., <i>et al.</i> 2016 [24]	Woman 12 years	Hepatic ducts	The lesion presented a fibrous hypocellular pattern, the ALK staining was positive, being observed at the cytoplasm level.	Treatment: surgical resection No recurrence was evidenced at 9 months of follow-up.
Liang Tang., <i>et al.</i> 2009 [25]	64: 42 men and 22 women Average: 49 years	Liver: Right lobe	The subtype predominated was myxoid (34 patients), followed by the compact spindle cell and the fibrous hypocellular one. ALK was not performed, only vimentin and actin staining that were positive, among other stains.	Treatment: surgical resection Up to 30 months of follow-up, no mortality was recorded in the study group

Table 1: Inflammatory myofibroblastic tumors located in the liver and/or bile ducts in adult and pediatric patients.

It is also important to mention that the symptoms as well as the radiological findings in these lesions are nonspecific, so the definitive diagnosis will be made through the histological examination [16]. Another repercussion is that due to this clinical presentation, lesions that are located in cavities are diagnosed when they involve adjacent organs.

At the liver and/or bile duct level, inflammatory myofibroblastic tumors could cause pain in the right upper quadrant, fever, general malaise, and weight loss, among the most frequent alterations [17,18].

Imaging characteristics

On imaging, it generally appears as a single mass, which captures contrast, although the presence of multiple small nodules has also been reported, in approximately 20% of cases, which in some cases replaced a complete lobe of the liver [26,27].

In general, the imaging characteristics of Inflammatory Myofibroblastic Tumors are nonspecific, as well as the clinical and laboratory characteristics, those that are located in the liver with extension of the bile ducts, it has been observed that in the ultrasound study they are characterized by being hypoechoic lesions, although also they can be hyperechoic. In the tomographic study, contrast uptake is observed in a heterogeneous manner, which may present areas of central necrosis. In resonance studies, they are hypointense in T1 and T2, enhancing after contrast administration [28].

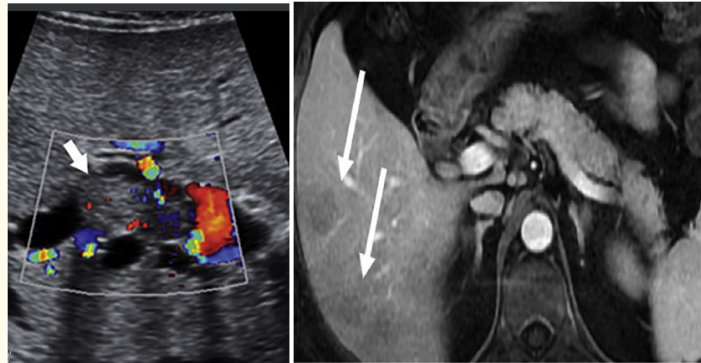


Image 1: A) Transverse Doppler ultrasound photograph showing an expandable mass with a soft tissue appearance (white arrow) within a dilated intrahepatic bile duct. B) Post-contrast images of the axial portal venous phase show focal nodular lesions (white arrows) within the right hepatic lobe that show an intermediate T2 signal, restricted diffusion, and mild enhancement after contrast administration. Source: Surabhi VR., et al [28].

In a study carried out by Zhao XT, et al. it was sought to determine the association between the tomographic characteristics and the histopathological subtypes of the Inflammatory Myofibroblastic Tumor, reporting 7 cases of the vascular myxoid subtype, 13 classified as cellular compact and 9 hypocellular fibrous cases. After the analysis, they concluded that there was no association between the tomographic findings and the histological type, for which they emphasized that the histological findings are fundamental, as well as the complement with immunohistochemical and even molecular studies. Recommending the usefulness of CT scans to assess the extent of this neoplasm in order to provide adequate treatment [29].

Laboratory alterations: Regarding laboratory tests, patients may show microcytic anemia, an increase in the erythrocyte sedimentation rate, thrombocytosis, this is mentioned as being due to the increased production of interleukin 6, a pro-inflammatory cytokine, however, it has not yet been known the pathophysiological mechanism that causes these alterations in the laboratory [12-18].

Macroscopic characteristics: The lesions appear solid, light brown in color and most are circumscribed [18,27]. Image 2 shows a lesion located at the level of the right hepatic duct measuring 3.5 x 3.0 x 1.7 cm with extension to the common hepatic duct and liver parenchyma.



Image 2: Photograph of a lesion at the level of the hepatic duct in a pediatric patient. This lesion is light brown in color, solid in appearance, and extends to the common hepatic duct and liver tissue. The initial differential diagnosis was to rule out Klatkstin tumor. Source: Prado-Cucho S, Huanca-Amesquita L [20].

Microscopic characteristics

Microscopically it is observed that they are made up of components, one of these consists of myofibroblastic cells, with an elongated or spindle cell appearance with an increase in the nucleus-cytoplasm ratio, nuclei with soft chromatin and the presence of an inconspicuous nucleolus, a second component is the stroma that can vary from having a myxoid appearance to being predominantly formed by collagen fibers that are arranged between the myofibroblastic cells and the third characteristic component is the inflammatory cells, among which lymphocytes and plasma cells are most frequently observed, eosinophils can also be seen [18].

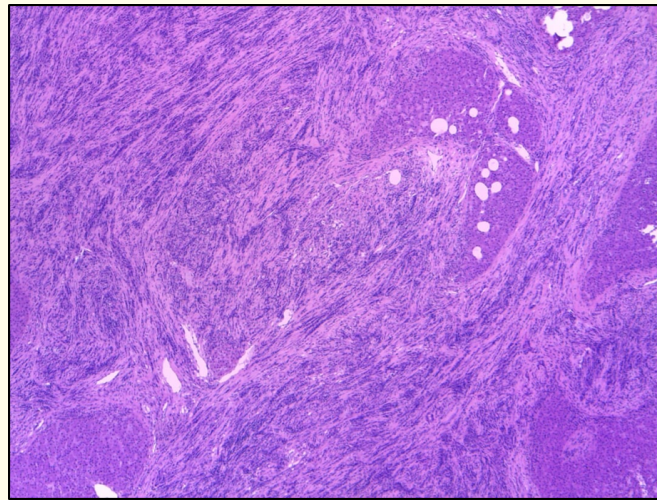


Image 3: Panoramic 4X microscopic photo with Hematoxylin-Eosin staining. A neoplasm that infiltrates the liver parenchyma is observed (*), the sample was sent and processed by freezing techniques, the descriptive diagnosis of fibrous proliferation and chronic inflammation was answered and it was referred to paraffin. Source: Prado-Cucho S, Huanca-Amesquita L [20].

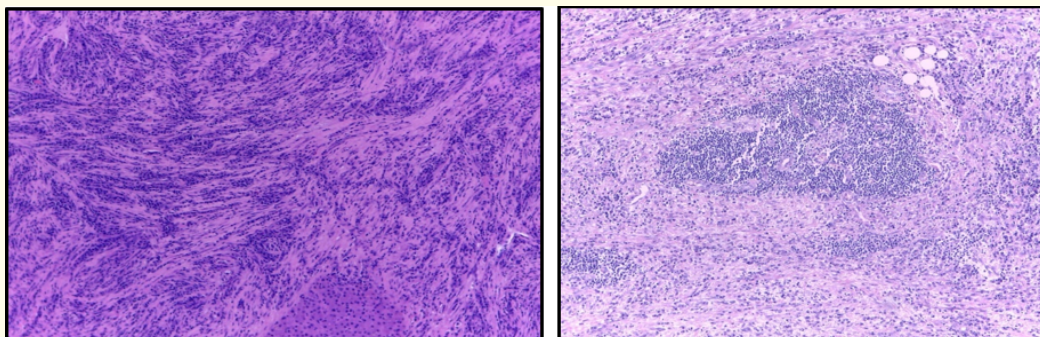


Image 4a and 4b: Microscopic photos at 10X magnification with Hematoxylin-Eosin staining. At a higher magnification in the images, the inflammatory cell component of the neoplasm stands out, which are diffusely arranged or can be grouped forming lymphoid accumulations. Source: Prado-Cucho S, Huanca-Amesquita L.

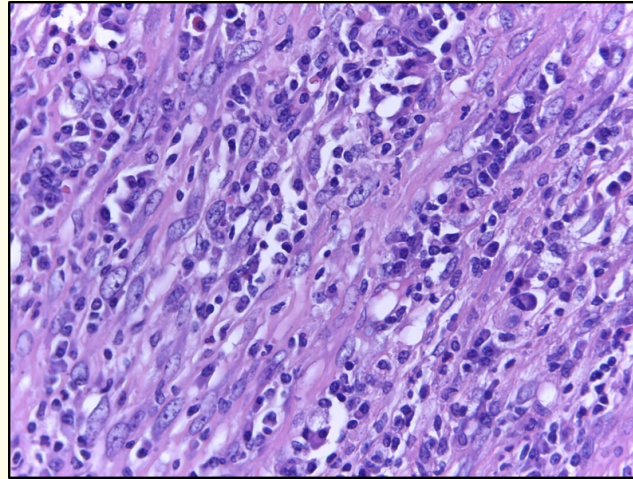


Image 5: Microscopic photo with a 40x magnification and Hematoxylin-Eosin staining. At higher magnification, the components of the neoplasm can be seen in greater detail: soft-looking spindle cells with inconspicuous nucleoli (red arrow), collagen fibers (blue arrow) and the inflammatory component with a predominance of lymphocytes and plasma cells, as well as few mast cells (green arrow). Source: Prado-Cucho S, Huanca-Amesquita L [20].

Depending on their arrangement, various patterns can be observed, which can occur in isolation or at the same time in various proportions in the same patient, the first of which consists of the presence of spindle cells in a myxoid or edematous stroma, being observed presence of thin vessels, calling this the vascular myxoid pattern. The second pattern consists of the presence of abundant spindle cells in an inflammatory background, this can be confused or we should make the differential diagnosis with fibromatosis, fibrous histiocytoma or smooth muscle neoplasms, it is called compact spindle cell pattern. The third pattern is characterized by the predominance of collagen fibers that could resemble a scar or various types of lesions with a fibrous component, differentiate from fibromatosis, this is called hypocellular fibrous pattern [1,7]. The diagnosis of this lesion is very challenging both from the clinical point of view as well as when performing the histopathological study of small samples by freezing techniques [2].

Cytological characteristics

There are few studies that describe the cytological characteristics of inflammatory myofibroblastic tumor, since the pattern and arrangement of the components of the neoplasm are more clearly appreciated in the histological study. However, when we are faced with a neoplasm located at the liver and/or bile duct level, less invasive studies are carried out at the beginning, such as fine needle aspiration biopsies (FNA), in which spreads will be observed cells with a spindle cell appearance, nuclei soft, surrounded by inflammatory cells, which could suggest that we consider this pathology as a differential diagnosis [13].

Another point that we want to highlight is the diagnosis made through biopsies, in the study by Dalton, *et al.* who analyzed 32 patients with lesions in different locations, 15 of these underwent preoperative biopsies, 7 with a needle and 8 incisional ones, of which 3 and 1 were incorrectly diagnosed respectively (nodular fasciitis, rhabdomyosarcoma and squamous metaplasia with infiltrated lymphohistiocytic) [30].

Immunohistochemical studies

Immunohistochemical techniques allow them to be differentiated from other entities, with positivity for ALK being one of the markers that characterizes this pathology, however it is positive in 50% of patients, in other cases it may present partial and inclusive staining that is absent [5,8-11,18,31]. Other stains that are positive in most cases but are less specific is the staining for actin and vimentin.

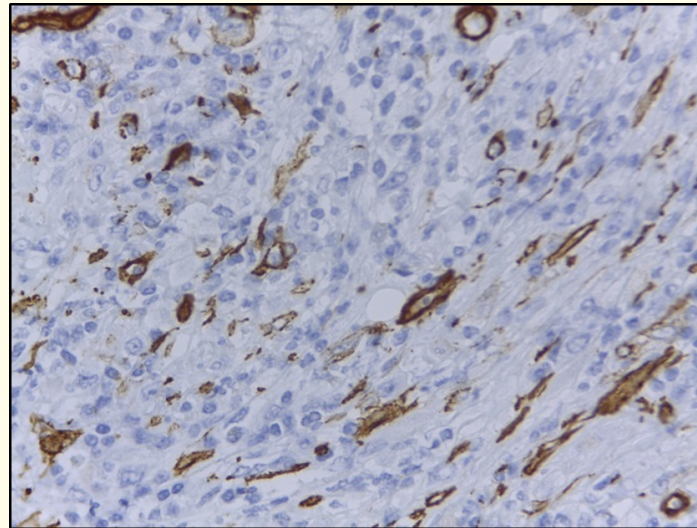


Image 6: Microscopic image of immunohistochemistry (IHC) 40X -Actin. The actin study is positive when it reflects a staining at the level of the membrane and cytoplasm, as is seen in the present photograph in which it is positively marking the myofibroblasts. Source: Prado-Cucho S, Huanca-Amesquita L [20].

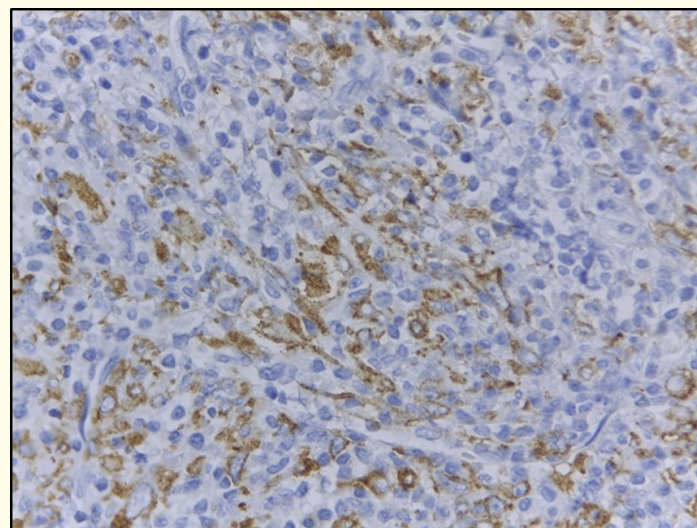


Image 7: Immunohistochemical microscopic image (IHC) 40X -ALK. The ALK staining that contributes to the diagnosis of inflammatory myofibroblastic tumor can present in various patterns, in this image a staining at the level of the membrane and cytoplasm is observed in the myofibroblasts. It is important to carry out this study since it corresponds to the expression of the most frequent genetic alteration of the inflammatory myofibroblastic tumor. Source: Prado-Cucho S, Huanca-Amesquita L [20].

Molecular alterations

As already mentioned, the main genetic alteration of the inflammatory myofibroblastic tumor consisted of the alteration of the ALK gene.

The ALK gene is located on the short arm of chromosome 2, at the 2p23.2 locus. This gene encodes a receptor tyrosine kinase, which belongs to the superfamily of insulin receptors. The protein comprises an extracellular domain, a hydrophobic stretch corresponding to a single-pass transmembrane region, and an intracellular kinase domain. The alteration of this gene occurs in approximately half of the cases, causing alteration in the tyrosine kinase pathway, however, several genes have currently been associated, including ROS, PDGFRB, NPM, TPM3, TPM4, TFG, ATIC, CLTC, MSN, RANBP2, CARS, SE31L1, NUMA1, EMLA4 [5,8-12,31,32].

Likewise, it has been observed that in lesions that are ALK negative, translocations have been recorded that compromise other ETV6-NTRK3 genes and other rearrangements and less frequent cases of RET [9,11].

The report of inflammatory myofibroblastic tumors has been recorded in the following studies.

Regarding ALK staining, López, *et al.* [33] reported that 11 of 12 cases were positive, observing different staining patterns, in the myxoid pattern 3 presented dot-like staining, 2 diffuse cytoplasmic and 1 case with granular cytoplasmic staining. It is important to analyze the type of pattern since it is associated with the fusion with different genes TPM3, TPM4, CARS, CLTC and RANBP2 and to take into account that the dot-like staining pattern has been associated with a round cell to epithelioid morphology and worse prognosis, however, not all health establishments carry out confirmation through genetic studies [33].

It is mentioned that when there is a fusion with the TPM3, TPM4, EML4 or SEC31L122 genes with the ALK gene, diffuse positive staining at the cytoplasmic level will be observed in the immunohistochemical study of ALK. While this will be granular cytoplasmic when alterations are observed with the CLTC gene, and the dot-like staining in relation to the modifications of the RANBP233 gene.

Differential diagnosis

Among the differential diagnoses we can mention gastrointestinal stromal tumors (GIST), malignant fibrous histiocytoma, rhabdomyosarcoma, solitary fibrous tumor, among the main [34,35]. However, in these lesions the inflammatory component is not a characteristic component.

While when this component predominates, it is also important to perform the differential with Hodgkin's lymphoma taking into account age, finally in this age group it is important to have inflammatory pathologies in the differential diagnosis.

In the study by López, *et al.* they propose a diagnostic algorithm based on the histological, immunohistochemical and molecular characteristics. To perform the histopathological diagnosis, the characteristics of the architecture pattern must be observed as well as the cytology, it is recommended to request an ALK immunohistochemical study, if this result is positive, a molecular FISH-ALK study must be carried out, if this result is positive It is diagnosed as Inflammatory Myofibroblastic Tumor, if the FISH study is negative, the NSG sequencing study should be carried out, which could result in alteration of the ALK, ROS1, PDGFRB gene, also being diagnosed as TMI. Whereas, if the NSG is positive, the alteration of the NTRK3 gene must be correlated with the morphology and consider excluding the diagnosis of Childhood Fibrosarcoma. If the NSG is negative, the lesion should be considered as a myofibroblastic proliferation to rule out pseudotumors. Similarly, NSG is recommended if ALK immunohistochemical staining is negative [23].

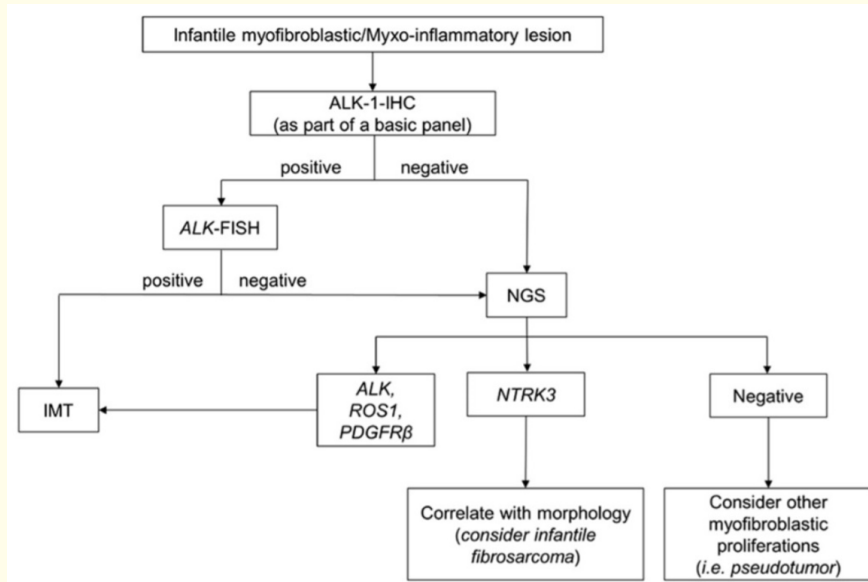


Image 8: Diagnostic algorithm. Source López, et al [23].

Treatment

The treatment of choice consists of surgical resection of the lesion with free margins of the neoplasm, however, taking into account the location of the lesion or if there is a residual lesion, systemic therapy is indicated, for this various treatments have been used: from steroids or chemotherapy, based on anthracycline/ifosfamide-based, or methotrexate and vinorelbine/vinblastine-based, however there is no consensus on this systemic therapy. Likewise, since 2010, clinical trials have been published reporting the use of crizotinib and ceritinib in patients with alteration of the ALK gene or with positive expression of ALK by immunohistochemical techniques [34-42].

Prognostic

Inflammatory myofibroblastic tumors can present local infiltration and even distant metastases after resection, it is mentioned that these events can occur in up to 5% of cases, this percentage would depend on the type of resection and the involvement of the surgical borders therefore, when it comes to a localized lesion with resection of lesion-free margins, the prognosis will be better [23].

Conclusion

As has been described, the clinical diagnosis of this pathology is a challenge, as well when studies of biopsies by fine needle aspiration or biopsies by freezing techniques are performed. For this reason, we consider it important to know the clinicopathological characteristics to be able to make the differential diagnosis of liver and bile duct lesions in pediatric patients, since this neoplasm and the aforementioned locations are rare.

Conflict of Interests

The author declares that there are no conflicts of interest.

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