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Epithelioid Inflammatory Myofibroblastic Sarcoma: Case Series With a First Report of *CLTC::ALK* Fusion in an Aggressive Disease

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ABSTRACT

Epithelioid inflammatory myofibroblastic sarcoma (EIMS) is a rare and clinically aggressive variant of inflammatory myofibroblastic tumor (IMT). It typically presents in children and young adults, often affecting the abdominal cavity. It is characterized by the presence of plump, polyhedral, and epithelioid cells, and a distinctive nuclear or perinuclear ALK staining on immunohistochemistry. Various ALK fusion partners have been identified in EIMS, including *RANBP2, RRBP1, EML4*, and *VCL*. In this report, we present four cases of EIMS involving the abdominal cavity, including the first case with a *CLTC::ALK* fusion, which has previously been associated only with nonaggressive IMT.

1 | Introduction

Inflammatory myofibroblastic tumor (IMT) is a locally aggressive mesenchymal neoplasm, with a tendency to recur locally and rarely metastasize. While it most commonly occurs in children and young adults, cases have been reported across a wide age range. It typically affects the mediastinum, retroperitoneum, abdominopelvic cavity, and lungs. Histologically, IMT is characterized by a proliferation of cytologically bland, spindle-to-ovoid-fibroblastic/myofibroblastic cells, intermixed with an inflammatory infiltrate, predominantly consisting of lymphocytes and plasma cells. *ALK* rearrangements are identified in up to 60% of cases, with several fusion partners reported, including *TPM3*, *TPM4*, *CLTC*, *EML4*, *RANBP2*, and *IGFBP5* [1–3]. Approximately 50% of IMTs are positive for ALK by immunohistochemistry (IHC), with a cytoplasmic and membranous staining pattern.

Epithelioid inflammatory myofibroblastic sarcoma (EIMS) is a rare variant of IMT, distinguished by its characteristic morphology and more aggressive clinical behavior. First described by Marino-Enriquez et al. in 2011, EIMS features plump polyhedral and epithelioid cells, with vesicular nuclei and conspicuous nucleoli, with eosinophilic to amphophilic cytoplasm, and a distinctive nuclear or perinuclear ALK staining pattern [4].

Gene rearrangements involving *ALK*, with fusion partners such as *RANBP2*, *RRBP1*, *EML4*, and *VCL*, have been reported in EIMS [4–7]. In this study, we present four cases of EIMS, including the first one with a *CLTC::ALK* fusion. This fusion has previously been reported only in nonaggressive IMT [2, 8]. While studies typically describe granular cytoplasmic staining for the *CLTC::ALK* fusion tumors, our case exhibited a perinuclear staining pattern for ALK on IHC, similar to EIMS with other more common fusions.

2 | Materials and Methods

2.1 | Case Selection

This study was approved by the Institutional Review Board of Indiana University. Three of the cases were identified through routine clinical practice at Indiana University Health, while one case was referred from Baylor Scott & White Health in Texas. The cases included were diagnosed between 2016 and 2024. The clinicopathologic features of each case were evaluated by the authors.

2.2 | IHC

A panel of immunohistochemical antibodies was performed for each case on available 4-μm formalin-fixed paraffin-embedded tissue sections using standard techniques. Detection and staining for all cases were performed using a fully automated diaminobenzidine antigen retrieval system (Benchmark ULTRA; Ventana Medical Systems, Tucson, AZ, USA), with appropriate controls. The following antibodies were used: mouse monoclonal anti-SMA (1A4, RTU; Dako), mouse monoclonal anti-desmin (D33, RTU; Dako), mouse monoclonal anti-myogenin (F5D, RTU; Dako), rabbit monoclonal anti-MyoD1 (EP212, RTU; Cell Marque), mouse monoclonal anti-human cytokeratin (AE1/AE3, RTU; Dako), rabbit polyclonal anti-S100 protein (RTU; Dako), mouse monoclonal anti-HMB45 (HMB45, RTU; Dako), monoclonal rabbit anti-ALK (D5F3, RTU; Cell signaling), mouse monoclonal anti-CD31 (JC70A, RTU; Dako), mouse monoclonal anti-CD34 (QBEnd 10, RTU, Dako), rabbit monoclonal anti c-kit (YR145, RTU; Cell Marque), mouse monoclonal anti-CD30 (Ber-H2, RTU; Dako), mouse monoclonal anti-CD10 (DAK-CD10, RTU; DAKO), mouse monoclonal anti-CD45RB/LCA (2B11 + PD7/26, RTU; Dako), mouse monoclonal anti-CD5 (4C7, RTU; Dako), mouse monoclonal anti-MDM2 (AB-1/IF2, 1:100; Cell Marque), mouse monoclonal anti-CDK4 (DCS-31, 1:25; Invitrogen), monoclonal mouse anti-human p53 protein (DO-7, RTU; Dako), monoclonal mouse anti-human calretinin (DAK-Calret 1, RTU; Dako), and monoclonal mouse anti-human podoplanin (D 2–40, RTU; Dako).

2.3 | Fluorescent In Situ Hybridization (FISH)

FISH study for ALK rearrangement was performed on Case 3 on a 4-μm-thick paraffin section with Vysis ALK Break Apart FISH Probe (Abbot Molecular Inc), based on the manufacturer's instruction. Cases 1 and 4 underwent FISH analysis for ALK rearrangement at the outside center, and the reports were subsequently reviewed.

2.4 | Next-Generation Sequencing

Cases 1 and 2 had molecular profiling performed through Caris Life Sciences. Whole exome sequencing with a high-throughput assay analyzed over 22 000 DNA genes, and RNA analysis via whole transcriptome sequencing (WTS) was used to enhance detection of genome-level alterations [9]. Case 4 had a translocation fusion assay performed at Mayo Clinic. However, in Case 3, sequencing studies were not performed due to limited available tumor material.

3 | Results

3.1 | Clinical Presentation

3.1.1 | Case 1

A 22-year-old female presented to an outside medical center with abdominal pain and a palpable abdominal mass. Magnetic resonance imaging (MRI) of the pelvis showed a large, lobulated intra-abdominal mass extending from the pelvis to the epigastric area. She underwent an exploratory laparotomy with resection of the pelvic mass, pelvic lymphadenectomy, and excision of the pelvic peritoneum. Histopathological examination, supported by immunohistochemical stains showing positive staining for desmin and smooth muscle actin (SMA), led to the diagnosis of leiomyosarcoma.

One month after the resection, the patient developed a recurrence, with numerous FDG-avid omental, peritoneal, and serosal deposits, along with massive ascites and bilateral anterior phrenic nodal metastases. Reassessment of the resected pelvic tumor, along with additional immunohistochemical stains, revealed positive ALK staining. FISH analysis confirmed *ALK* gene rearrangement. The patient was treated with a cycle of gemcitabine and crizotinib.

She later presented to our center with worsening symptoms and diffuse peritoneal disease on CT imaging of the abdomen and pelvis. Fine needle aspiration (FNA) and core biopsy of the peritoneal mass confirmed the diagnosis of EIMS. She is stable on crizotinib, with a recent CT scan showing no evidence of recurrent disease (Table S1).

3.1.2 | Case 2

A 14-year-old female with a month-long history of abdominal pain and a mass was found to have a large left adnexal mass on ultrasound, suggesting an ovarian teratoma. A CT scan of the abdomen and pelvis revealed a 20 × 7 × 11 cm soft tissue mass with peritoneal implants. An ultrasound-guided FNA biopsy diagnosed EIMS. She received 13 cycles of crizotinib, achieving complete remission.

However, 6 months after stopping crizotinib, she had a recurrence with a 7.5 × 5.3 cm mass in the left paracolic gutter, compressing the left colon. She underwent resection of the mass and a portion of the left colon. Crizotinib was resumed, and after 12 treatment cycles, there is no evidence of recurrence to date.

3.1.3 | Case 3

A 70-year-old male presented with a lower abdominal mass accompanied by fever, rash, and hypercalcemia. Abdominal CT imaging revealed an 18.6 × 13.3 cm mass in the left hemiabdomen with complex, heterogeneous, peripheral internal

calcification involving the splenic flexure of the colon. FNA biopsy diagnosed the mass as EIMS. He underwent tumor resection, but recurrence occurred 2 months later as an enlarging mass at the resection site measuring 18 × 10 × 19 cm. Managed with chemotherapy and crizotinib, he developed right-sided hemiplegia from a stroke and chose hospice care, discontinuing crizotinib. Further follow-up was not obtained.

3.1.4 | Case 4

A 36-year-old male presented with abdominal pain. Abdominal CT imaging revealed a large intra-abdominal mass attached to the small bowel, measuring 16.9 × 15 × 13.2 cm (Figure 1A), along with multiple peritoneal masses. He underwent exploratory laparotomy with resection of the abdominal tumor. Following confirmation of the diagnosis of EIMS, the patient is receiving crizotinib, with no evidence of disease at 16-month follow-up.

3.2 | Morphologic, Immunohistochemical, and Genetic Findings

On gross examination, tumors in Cases 2–4 were large soft tissue masses adherent to the bowel, with solid, nodular cut sections showing hemorrhage and necrosis. Case 4 had a solid homogeneous cut section (Figure 1B). FNA and core biopsies were obtained in Case 1. The FNA smears were hypocellular, consisting of few atypical epithelioid cells.

Histology of all cases showed large atypical epithelioid cells with eosinophilic cytoplasm, vesicular nuclei, prominent nucleoli, and inflammatory infiltrates, mainly neutrophils (Figure 1C). Spindle cell components, myxoid to collagenous stroma, and mixed inflammatory infiltrates including neutrophils, lymphocytes, and plasma cells were also noted. Mitotic figures were rare (1 per 10 HPF), and necrosis was present in all cases.

In Case 1, tumor cells were positive for desmin, SMA, CKAE1/AE3 (focal), and CD10, but negative for CD30, CD45, and CD5. Case 2 showed positivity for SMA and CD30, and negativity for CKAE1/AE3, myogenin, desmin, MyoD1, and HMB45. Case 3 had positive staining for desmin, SMA, and CKAE1/AE3, and negative for CD31, CD34, S100, myosin, and C-KIT. Case 4 was positive for desmin, focally positive for SMA and CD30, and negative for CKAE1/AE3. All four cases were positive for D2-40, showing focal to diffuse membranous positivity (Figure 1D). Calretinin staining was focally weak cytoplasmic to nuclear positive in Cases 1, 2, and 4 (Figure 1E) and negative in Case 3. Case 4 also showed positive staining with CDK4 and focal staining with MDM2. All four cases exhibited strong nuclear membranous/perinuclear staining with ALK (Figure 1F) (Table S2).

FISH analysis was done in Cases 1, 3, and 4 and was positive for ALK gene rearrangement [inv (2)(p21;p23)] in all three cases.

Next-generation sequencing of RNA isolated from the tumor sample identified a pathogenic *CLTC::ALK* fusion in Case 1 (Figure 1G) and *RANBP2::ALK* gene fusion in Cases 2 and 4. Additionally, NGS of DNA revealed a *TP53* mutation, specifically the c.817C>T (p.Arg273Cys) variant in Case 2. Assessment for TP53 mutation in the remaining three cases was performed using p53 IHC, which showed scattered, weak nuclear staining consistent with a wild-type (nonmutant) pattern in all cases. However, in Case 3, the ALK fusion partner could not be identified, as sequencing studies were not performed due to limited available tumor material.

4 | Discussion

EIMS is a rare and aggressive variant of IMT. While IMTs are commonly found in the lungs and abdominopelvic region, EIMS more frequently presents as an intra-abdominal mass. However, other sites such as the lungs, uterus, ovaries, brain, and larynx have also been reported [7, 10–12]. EIMS primarily affects children and adolescents and has a male predilection, in contrast to the conventional IMT, which has a slight female predominance. The exact incidence of EIMS is likely underestimated, due to its rarity and limited recognition.

The reported age of presentation for EIMS ranges from 4 months to 76 years (mean age of 31.6 years) [13, 14]. As these tumors commonly involve the abdominal cavity, the patients often present with abdominal pain and discomfort, and, in some cases, ascites (https://www.sciencedirect.com/topics/medicine-and-dentistry/ascites).

Histologically, EIMS is characterized by: (a) polyhedral to epithelioid tumor cells, with vesicular nuclei, and prominent nucleoli with eosinophilic to amphophilic cytoplasm; (b) myxoid stroma admixed with an inflammatory infiltrate frequently composed of neutrophils, although lymphocytes and eosinophils can also be observed; and (c) unique nuclear or perinuclear staining pattern of ALK by IHC. Plasma cells are typically absent, which distinguishes EIMS from IMT. A minor spindle cell component and necrosis can be observed, along with variable mitotic activity [4, 15].

Immunohistochemically, the tumor cells can show variable positivity for desmin, SMA and CD30. Li et al. [16] described the immunohistochemical staining pattern of 20 reported cases of EIMS, finding desmin to be positive in 100% of cases (13/13), SMA in 33% (5/15) and CD30 in 69% (9/13) of cases. EIMS are typically negative for myogenin, S100, CD117, DOG1, and CD34 [16]. Cases positive for pan-cytokeratin and EMA staining have been reported [15, 16]. Unlike IMT, which shows cytoplasmic and membranous staining for ALK, most cases of EIMS demonstrate nuclear membranous staining [4]. In some cases, cytoplasmic staining with perinuclear accentuation can also be observed, depending on the fusion partners involved [5, 16].

A supportive feature of EIMS is the presence of ALK gene rearrangements, which are found in the majority of cases. The *RANBP2::ALK* is the most frequent fusion reported to date in cases of EIMS, resulting in a characteristic nuclear membranous ALK staining pattern [4]. Besides *RANBP2::ALK* fusion, EIMS has been described with several other ALK fusion partners, including *RRBP1::ALK, EML4::ALK, VCL::ALK, STRN::ALK*, and *PRRC2B::ALK* [5–7, 17, 18] (Table 1). Further, a *ROS1::TFG* fusion was noted in one case of EIMS from a series of 12 pediatric

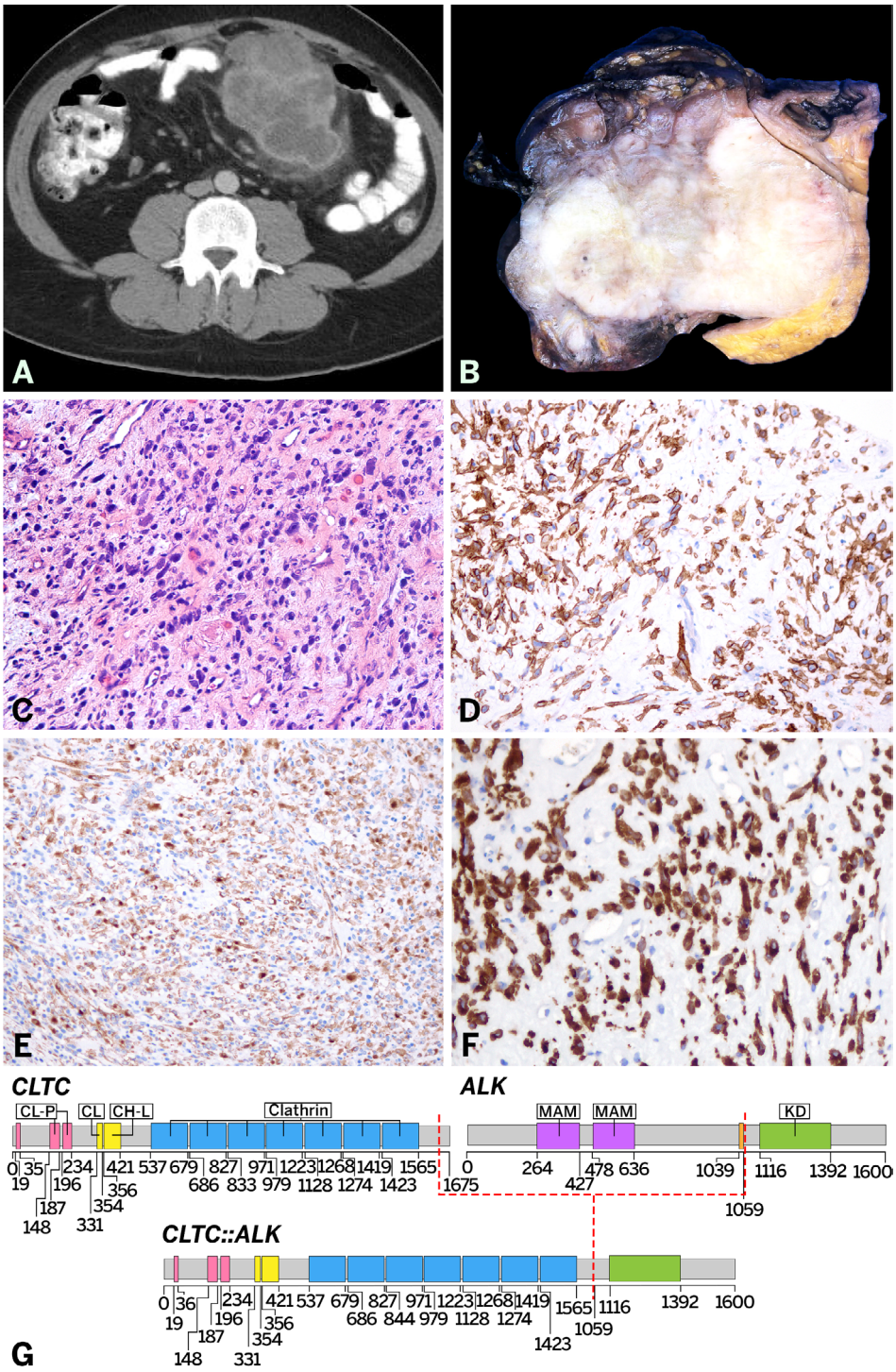

FIGURE 1 | (A) Abdominal CT imaging of revealing intrabdominal mass. (B) Tan-white mesenteric mass with solid homogenous area and ill-defined border adherent to the small bowel. (C) Core biopsy of the tumor in Case 1 showed round, epithelioid tumor cells with large nuclei and prominent nucleoli (hematoxylin and eosin, ×200). (D) D2-40 IHC in Case 1 showing diffuse membranous staining (×200). (E) Calretinin IHC in Case 2 showing weak cytoplasmic staining with focal nuclear staining (×200). (F) ALK IHC in Case 1 showed perinuclear staining pattern (×400). (G) Molecular findings. In Case 1, next-generation RNA sequencing revealed gene fusion involving exon 31 of CLTC (chr17:59690711) and exon 20 of ALK (chr2:29223528). CH-L clathrin H link; CL clathrin link; CL-P clathrin propel; KD kinase domain; MAM meprin/A-5 protein/receptor protein-tyrosine phosphatase mu.

cases reported by Cheng et al. [10] In our study, FISH revealed ALK gene rearrangement in three cases. Sequencing detected gene fusions in three cases: two had *RANBP2::ALK* fusion, and one had *CLTC::ALK* fusion, which is previously unreported in EIMS.

CLTC::ALK fusions have been reported in IMT and ALK-positive lymphomas with granular cytoplasmic staining with ALK on IHC [2, 22]. CLTC stands for the clathrin heavy chain gene, located on chromosome 17q23, which encodes the two heavy chains of clathrin—a major structural protein of coated

TABLE 1 | Summary of reported ALK gene fusions in epithelioid inflammatory myofibroblastic sarcoma (EIMS) cases.

Study	Number of cases	Age	Gender	Site	ALK IHC	ALK gene rearrangement (FISH)	ALK fusion partner
Marino-Enriquez et al. [4]	11	7 months to 63 years	10 M 1 F	Intrabdominal	NM (9/11) Cytoplasmic with perinuclear accentuation (2/11)	Present (9/11)	*RANBP2* (3/11)
Lee et al. [5]	5	26–76 years	3 M 2 F	Intrabdominal 4/5 Liver 1/5	NM (2/5) Cytoplasmic with PN accentuation (3/5)	Present (5/5)	*RANBP2* (2/5) *RRBP1* (3/5)
Jiang Q et al. [6]	1	45 years	M	Intrabdominal	Cytoplasmic with prominent under nuclear membrane	Present	*EML4*
Chopra et al. [7]	1	72 years	F	Brain	Cytoplasmic and membranous	Present	*VCL*
Cheng et al. [10]	12	6–97 months	7 M 5 F	Intrabdominal 8/12chest 2/12 Throat 1/12 Maxillofacial 1/12	NM	Present (8/12)	*RANBP2* (1/8)
Singh et al. [11]	1	25 years	M	Right lung	Cytoplasmic with perinuclear accentuation	Present	NA
Collins et al. [12]	1	43 years	F	Uterus	Perinuclear	Present	*RANBP2*
Dou et al. [13]	1	70 years	M	Intrabdominal	NA	Present	NA
George et al. [14]	1	33 years	M	Intrabdominal	Cytoplasmic and PN	Present	*RANBP2*
Yu et al. [15]	5	15–58 years	2 M 3 F	Intrabdominal 5/5	NM (4/5) Cytoplasmic with PN accentuation(1/5)	Present (5/5)	NA
Li et al. [16]	1	31 years	M	Intrabdominal	NA	Present	*RANBP2*
Li et al. [17]	1	Middle aged	M	Stomach	Cytoplasmic	NA	*STRN*
Wang et al. [18]	1	42 years	F	Intrabdominal	NM	Present	*PRRC2B*
Wu et al. [19]	1	47 years	F	Intrabdominal	NM	Present	*RANBP2*
Fu et al. [20]	1	21 years	M	Left lung	Cytoplasmic	Present	NA
Kimbara [21]	1	22 years	M	Pelvic cavity	NM	NA	*RANBP2*
Present study	4	14–70 years	2 M 2 F	Abdomino-pelvic cavity	NM	Present (3/4)	*RANBP2* (2/3) *CLTC* (1/3)

Abbreviations: F, female; M male; NA, no data available; NM, nuclear membrane; PN, perinuclear staining.

vesicles involved in selective protein transport [2]. The fusion of *CLTC* with *ALK* leads to constitutive activation of the ALK kinase domain, contributing to the tumor's pathogenesis [2].

One case of IMT with CLTC-ALK fusion exhibited cytoplasmic, perinuclear, and punctate ALK staining [23]. Another case of IMT with CLTC-ALK fusion had spindle tumor cells with large ovoid nuclei, prominent nucleoli, inflammatory infiltrate rich in neutrophils, rare plasma cells, and scant necrosis, morphology similar to our case [24]. On IHC, ALK showed granular cytoplasmic positivity, whereas in our case, ALK staining was perinuclear.

Diagnosing EIMS can be challenging due to its rarity, especially on core biopsies. Differential diagnoses include myxoid leiomyosarcoma, GIST, ALCL, germ cell tumors, melanoma, myxoid and dedifferentiated liposarcoma, and other high-grade epithelioid sarcomatous tumors based on clinical presentation and histological features. ALK staining helps but is not definitive, as ALCL and other mesenchymal tumors can also express ALK [25]. *CLTC::ALK* fusion can complicate differentiation between EIMS and ALCL. In Case 1 of our study, the tumor was positive for desmin, SMA, and perinuclear ALK staining, but negative for CD30, EMA, CD45, and CD5, supporting EIMS diagnosis.

In this study, all four cases were large intraabdominal masses with morphology consistent with EIMS. Immunohistochemical analysis showed positivity for SMA in all tumors, desmin in three, and cytokeratin in two. All cases were ALK-positive with characteristic perinuclear staining patterns. One case had CDK4 and focal MDM2 positivity, suggesting a differential diagnosis of dedifferentiated liposarcoma, but *RANBP2::ALK* fusion confirmed EIMS. All cases showed D2-40 positivity, and three had weak calretinin staining, which may present a diagnostic pitfall for mesothelioma, particularly given the intra-abdominal location of the tumors.

Regarding the clinical behavior of EIMS, studies have shown that these tumors tend to behave aggressively, with documented cases of recurrences and metastasis. Metastatic spread to the bones, liver, spleen, and small intestine has been reported in several case studies [19, 20]. The reported median overall survival is 11–12 months (12 months-36 months) [15, 17]. Multiple studies suggest that the aggressive course of the disease may be linked to factors such as abdominopelvic/intraperitoneal origin, large tumor size, epithelioid morphology, and *RANBP2::ALK* fusion [13, 15].

Although there is no standardized management approach, tumors managed with surgical resection with clear margins, followed by ALK inhibitor therapy, have demonstrated a complete response [21]. Incomplete tumor resection is associated with a higher probability of recurrence. Resistance to ALK inhibitors can develop, particularly due to mutations such as ALK R1192P, which causes crizotinib resistance [18].

In our study, three of four cases presented with recurrence, but none metastasized. Three of the cases were managed with surgical resection followed by crizotinib therapy. One case was initially managed conservatively with crizotinib therapy but underwent surgical resection due to recurrence and resumed crizotinib. Following crizotinib therapy, no recurrence has been noted in three cases over the period of 9 months to 12 years, while one case was lost to follow-up.

5 | Conclusion

The study presents four cases of EIMS, including one with a CLTC::ALK fusion, previously linked to IMT. This case showed clinical features similar to EIMS cases with RANBP2::ALK fusion and responded completely to crizotinib treatment. Distinguishing EIMS from ALK-positive ALCL is challenging due to shared *CLTC::ALK* fusion. Accurate diagnosis of EIMS requires comprehensive immunohistochemical and molecular testing. New genetic alterations and fusion partners are expanding our understanding of EIMS, highlighting the importance of integrating molecular, morphologic, and immunophenotypic data for prognosis and treatment strategies.

Author Contributions

Concept, design, and coordination: D.M. and S.S. Compilation and analysis of clinicopathologic and clinical data: D.M., S.S., C.D., and A.A. Article draft, table, and figures: D.M., A.A., and R.B. Cases and/or intellectual contributions (including article editing): All authors.

Ethics Statement

This study was approved by the Institutional Review Board of Indiana University School of Medicine.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.