Misdiagnosis of inflammatory myofibroblastic tumor as primary pulmonary myxoid sarcoma: A case report

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Case Report

Keywords: Lung tumor, Inflammatory myofibroblastic tumors (IMT), primary pulmonary myxoid sarcoma (PPMS), Diagnosis, ALK, Prognosis

Posted Date: June 16th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1740048/v1

Abstract

Introduction: Inflammatory myofibroblastic tumors (IMTs) are intermediate biologic neoplasms, whereas primary pulmonary myxoid sarcoma (PPMS) is a rare mesotogenic tumor. However, when pulmonary inflammatory myofibroblastoma occurs with multiple complex pathological histologies, the two diseases can be easily misdiagnosed because of the similarity in the pathological features of both conditions. This phenomenon is a potential diagnostic trap.

Case presentation: IMTs with a mass in the left upper lung were reported in a 12-year-old patient. The patient did not exhibit fever, cough, hemoptysis, or chest pain. Surgical excision revealed that the tumors exhibited complex histological morphology. In the abundant myxoid matrix, spindle, ovoid and stellate tumor cells were closely arranged and exhibited negative immunohistochemistry desmin. Second-generation genetic sequencing revealed ALK–TPM3 gene fusion and absence of EWSR1–CREB1 gene fusion. Fluorescence in situ hybridization revealed positive ALK rearrangement and negative EWSR1 rearrangement. At the five-month follow-up after the operation, the patient exhibited recurrence of pathological conditions. The patient died a month after the follow-up.

Conclusion: IMT occurrence in the lungs and with pathological histology of more than two forms can result in misdiagnoses as PPMS. Furthermore, the tumor size, ALK–TPM3 gene fusion, and histological morphology difference may be related to poor prognosis.

Introduction

Inflammatory myofibroblastic tumor (IMT) is a rare low-grade malignant mesolobtogenic tumor that is typically observed in the lungs of children, adolescents, and women [1, 2]. IMTs can be locally invasive and are associated with distant metastasis in approximately 10% of cases [3, 4]. However, IMT prognosis is accurate and has a 5-year survival rate of 74–91% [5]. By contrast, primary pulmonary myxoid sarcoma (PPMS) is a rare mesolobar-derived tumor with fewer than 30 cases reported in literature [6]. In case of complex pulmonary inflammatory myofibroblastoma with multiple pathological histologic morphology, both diseases are possible because of similar pathological characteristics. Key identification elements are yet to be reported in literature. In this study, we report that clinicopathological features, diagnostic process, and IMT prognosis can be easily misdiagnosed as PPMS. The results of the study can improve clinical and pathologist awareness of both diseases and identify possible factors of poor disease prognosis.

Case Presentation

A 12-year-old girl was referred to our hospital because a physical examination revealed masses in the left upper lobe of her lung. The patient did not exhibit symptoms of pneumonia or any other respiratory obstructions. The patient was asymptomatic and denied exposure to toxins or infectious agents. Furthermore, family-related genetic history of the related disease was not reported. Obvious abnormalities

were not observed during general physical or laboratory examinations. A computed tomography (CT) image of the left superior lobe revealed a peripheral solid mass of approximately 8.8 cm × 6.7 cm and moderate nonuniform heterogeneous enhancement and edge blur (Fig. 1A). The observed mass indicated an obliteration of the bronchus and shallow lobulation. The interlobar tumor was pathologically diagnosed by using the puncture technique. Subsequently, surgical excision was performed after admission to our hospital. However, local recurrence was observed in the patient during the five-month follow-up after surgery. The patient was fatigued and coughing. CT revealed an extensive mass in the left chest cavity, which protruded to the lower part of the left chest wall muscle, left pleural effusion, and left atelectasis (Fig. 1B). Clinical diagnosis revealed a recurrence of left PPMS after the operation. The patient returned to the hospital again to receive chemotherapy for a month but the disease was not under control and the patient died a month after discharge. The patient survived only 190 days after definite diagnosis.

On a macroscopic level, the upper lobe of the left lung was 15 cm × 9 cm × 5 cm, mucinous, with a white and gelatinous nodule of approximately 9 cm × 6 cm × 5 cm. The tumor boundary was blurred, lobulated, and did not invade the bronchus (Fig. 2). On the microscopic level, the tumor contained a series of short ovoids and stellate cells. The cells were attached to the reticular fibers of the myxoid stroma and arranged in filaments and cords. Rare mitotic figures and poor lymphoplasmacytic cell infiltration was observed(Fig. 3–4). The tumor cells were slightly atypia, and the large partial nuclear fission was < 5/10 HFP in most regions. In the peripheral region of the tumor, the observed alveolar cells were all considered within normal levels (Fig. 5). Immunohistochemistry staining for distinguishing antigens revealed that the tumor cells were diffusely positive for vimentin(Fig. 6), CD68, and ALK and focally positive for epithelial membrane antigen (EMA). However, the cells were negative for rhabdoid cells, desmin, thyroid transcription factor-1 (TTF-1), cytokeratin 7 (CK7), S-100, CD34, CEA, STAT6, CgA, Syn, and cytokeratin (CK). Furthermore, the Ki-67 proliferation marker used to predict prognosis was 20%. Next-generation sequencing for genetic testing revealed ALK–TPM3 gene fusion, whereas EWSR1–CREB1 gene fusion was not observed. To verify the accuracy of the results, the fluorescence in situ hybridization (FISH) test was performed on tumor tissue that was preserved by formalin and embedded into paraffin. The results revealed an ALK translocation occurred because of the split red and green signals on the ALK break-apart probes (Fig. 7). However, red and green signal divisions were not observed on the EWSR1 separation probe (Fig. 8). Thus, pathological diagnosis was IMT.

Discussion

IMT is historphologically diverse and exhibits the following three basic histological morphologies [7]: □ the mucus-type pattern: the tumor stroma is mucoid and similar to nodular fasciitis; □ the cellular compact spindle cell pattern: a dense bundle of spindle fibroblasts and myofibroblasts were evident, with infiltration of histiocyte-like cells and inflammatory cells; and □fiber-type pattern: a sparse arrangement of tumor cells and an interstitium with various degrees of collagen, calcification, gravel and ossification. Immunohistochemistry results revealed the following. The tumor cells express SMA and vimentin, partially express desmin, CD34, CD68, and ALK, and do not express CK or S100. Abnormal ALK expression and ALK gene rearrangement represent a pathological histological diagnosis and differential

diagnosis, and ALK rearrangement was observed in approximately 50% of patients [8]. Among them, aberrant ALK expression and ALK gene rearrangement have pathological histological diagnosis and differential diagnostic significance. In 1999, Nicholson et al first described PPMS as a novel low-grade malignant myxoid endobronchial neoplasm [9]. Thway et al labeled this rare but unique myxoid tumor in 2011 as “primary pulmonary myxoid sarcoma (PPMS)” [10]. Since then, 28 instances of PPMS have been reported. To date, this disease has not been reported in minors. PPMS is an exceptionally rare intrapulmonary tumor emerging from large bronchi in young adults averaging 46.3 years old with female predominance (female: male, 1.5:1) [6.11]. Although the tumor was considered to have a distinct prognosis, renal metastasis, brain metastasis, and contralateral lung metastasis were observed in a few cases [10.12.13]. Clinical and imaging of the disease are yet to detailed specificity of PPMS. Diagnosis primarily depends on tissue morphology and genetic characteristics. The tumor was 1.5 to 13.0 cm in size, with the median size of 3.5 cm and a well-circumscribed nodular mass with clear boundaries. The cut surface was grayish-white, grayish-yellow, and gelatinous [6].Microscopic oval, spindle, or stellate shaped tumor cells embedded in a prominent mucinous matrix [9.10] are [10] characterized by the oncogenic fusion gene EWSR1–CREB1, which has been incorporated into the latest WHO guideline as a feature of this tumor [14]. However, in our case, histomorphology was very similar to PPMS, especially the tumor lobulated, microscopic nonrich mucus matrix with large astroand polygonal cells, small infiltration of inflammatory cells, and negative immunohistochemical desmin. Thus, accurate diagnosis becomes challenging. Second-generation sequencing of the cases revealed that the tumor was accompanied by ALK–TPM3 gene fusion, whereas EWSR1–CREB1 gene fusion was absent. The accuracy of the results was verified by the FISH test again, which revealed positive ALK gene rearrangement and negative EWSR1 rearrangement. Combining genetic testing and patient age, the diagnosis was IMT.

Differential diagnosis of the IMT of the lung includes gastrointestinal stromal tumor (GIST), leiomyoma, and fibromatosis [15]. □ Primary myoepithelial tumors of the lung in which cells have a reticulate and trabecular growth pattern and a prominent mucoid matrix. Tumor cells differ from spindle to epithelioid, with pale stained nuclei, eosinophilic, and clear cytoplasm. Myooepitheliomas in the lung are rare and can distinguish IMT through positivity for cytokeratin, S100, and other myoepithelial markers. □ Fibromatosis (Fibromatosis): more myofibroblasts observed in the lesion; however, the cells were arranged in parallel wide bundles, slightly wavy bending. The peripheral infiltration surrounds the skeletal muscle and is closely related to the tendon and aponeurosis. The inflammatory cell infiltration was less diffuse than IMT, positive for CD34 and catenin, and did not express SMA and MSA. □ External gastrointestinal stromal tumors in mesenteric, omentum, or retroperitoneal: nuclear vacuoles, rich in thick parenchyled vessels, positive for immunohistochemical markers CD117 and CD34, and negative for SMA. Shin et al[16] reported a case of GISTs concurrent with gastritis myofibroblastoma and detailed the first copresence of these two tumor components.□ Leiomyoma: the boundary is clear, with rich eosinophilic fiber cytoplasm, smooth muscle tumor cells exhibiting regular arrangement, woven, and no obvious inflammatory cell infiltration; immunohistochemistry can assist differentiation.

Previously, IMT of lung was considered to have a prognosis in the past, and in most cases, patient may exhibit tumor-free survival. The disease may be caused by infection or chronic inflammatory stimuli,

allergies, autoimmune disorders, and other factors [17]. In the reported case, the child had a large tumor, and two histological forms, with nonrich mucoid matrix, exhibiting a close bundle arrangement of spindle fibroblasts and myofibroblasts and no obvious inflammatory cell infiltration. Immunohistochemical tumor cells of vimentin (+), EMA (+), ALK (+), and SMA (+), but no desmin, result in a poor prognosis. This phenomenon was seldom reported previously. Therefore, we speculate histologic morphology and tumor size may be related to various clinical outcomes. Furthermore, ALK is a tyrosine kinase receptor, and ALK expression and gene rearrangement plays a crucial role in the genesis of inflammatory myofibroblastoma [18]. ALK gene rearrangements typically occur in children and young adults, and the ALK gene is fused to two related tropomyosin genes, namely TPM3 and TPM4. Epithelioid inflammatory myofibroblastic sarcoma is a subtype of IMT, which can appear as ALK nuclear membrane and perinuclear expression, aggressive biological behavior, rapid local recurrence and often death [19]. In this case, ALK–TPM3 gene fusion has a very poor prognosis. We speculate if this gene fusion also a molecular marker indicating poor prognosis. Li et al reported two patients with ALK–RANBP2 inflammatory myofibroblastoma with rearrangement still died within a short time [20]. However, because of the limited number of cases, future studies should focus on the confirmation of the phenomenon.

Currently, IMT is a less malignant mesenchymal tumor that typically occurs predominantly in children or adolescents. Tumor-free survival has been reported in most cases, and recurrence and distant metastasis have been reported in few cases. However, in the reported patient poor prognosis may be related to the tumor size, complex histological morphology, and ALK-TPM3 gene fusion. However, because of the small number of cases, conclusion are definite. To date, surgical resection remains the preferred treatment for IMT because of conventional chemotherapy or radiotherapy reporting poor efficacy. In previous reports, limited studies have focused on distinguishing PPMS from IMT. When a combination of IMT with non-mucus-rich matrix and limited inflammatory cells is reported, misdiagnosis and missed diagnosis of PPMS should be avoided. Genetic testing can improve diagnosis and differential diagnosis.

Abbreviations

CT: Computed tomography.

Declarations

Ethics approval and consent to participate

This case report was approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University. Written informed consent was obtained from the patient for publication of this clinical case report.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of data and materials

All the data regarding the findings are available within the manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

None

Authors' contributions

Resources: Xiang Huang, Shuai Luo, Yao Li. Writing–original draft: Xiang Huang. Writing-review & editing:Xiang Huang, Jinjing Wang. All the authors have read & approved the final manuscript.

Acknowledgements

The authors would like to thank AJE (American Journal Experts) for English language editing.

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Figures

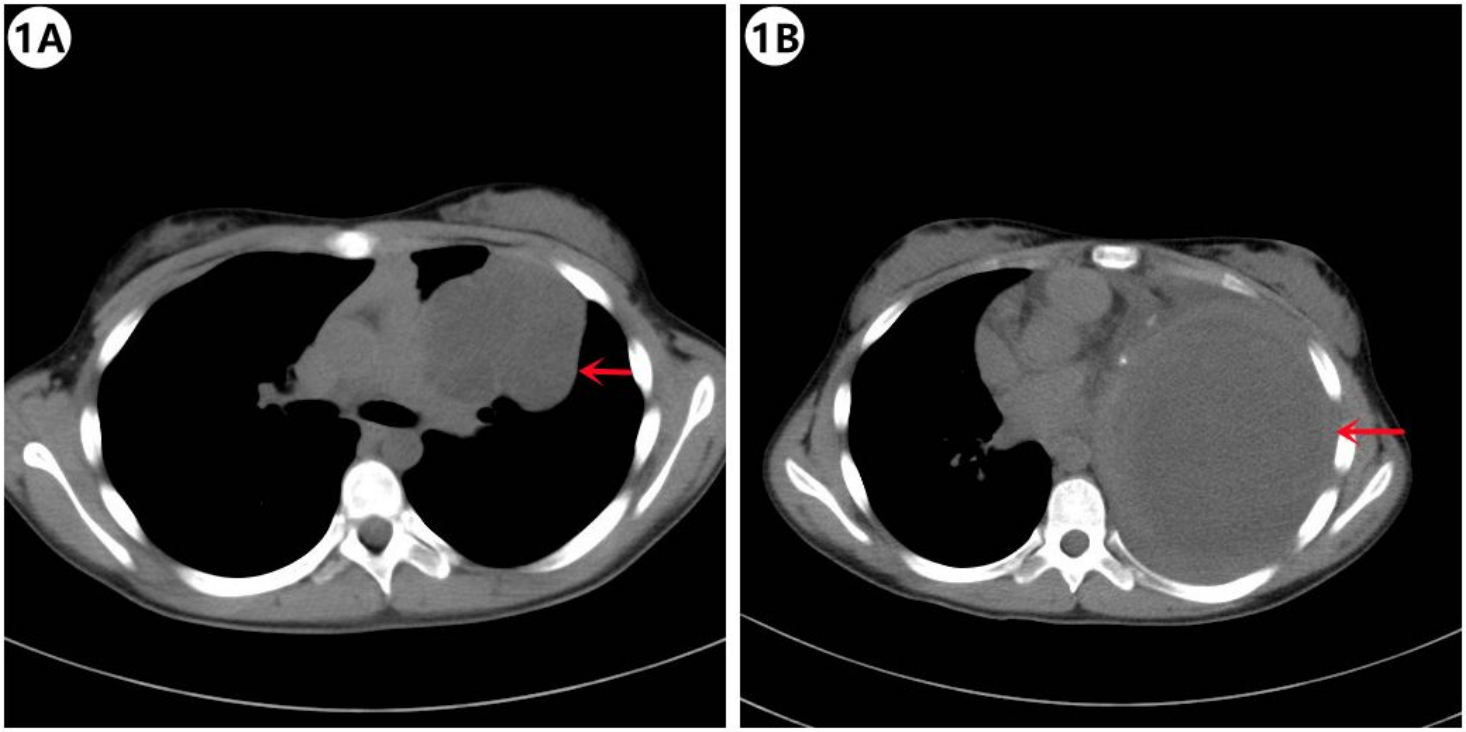

Figure 1

1A The computed tomography (CT) image of the left superior lobe revealed a peripheral solid mass of approximately 8.8 cm × 6.7 cm and moderate nonuniform heterogeneous enhancement and edge blur .

1 B CT revealed an extensive mass in the left chest cavity, which protruded to the lower part of the left chest wall muscle, left pleural effusion.

Figure 2

The white and gelatinous nodule of approximately 9 cm × 6 cm × 5 cm. The tumor boundary was blurred, lobulated, and did not invade the bronchus.

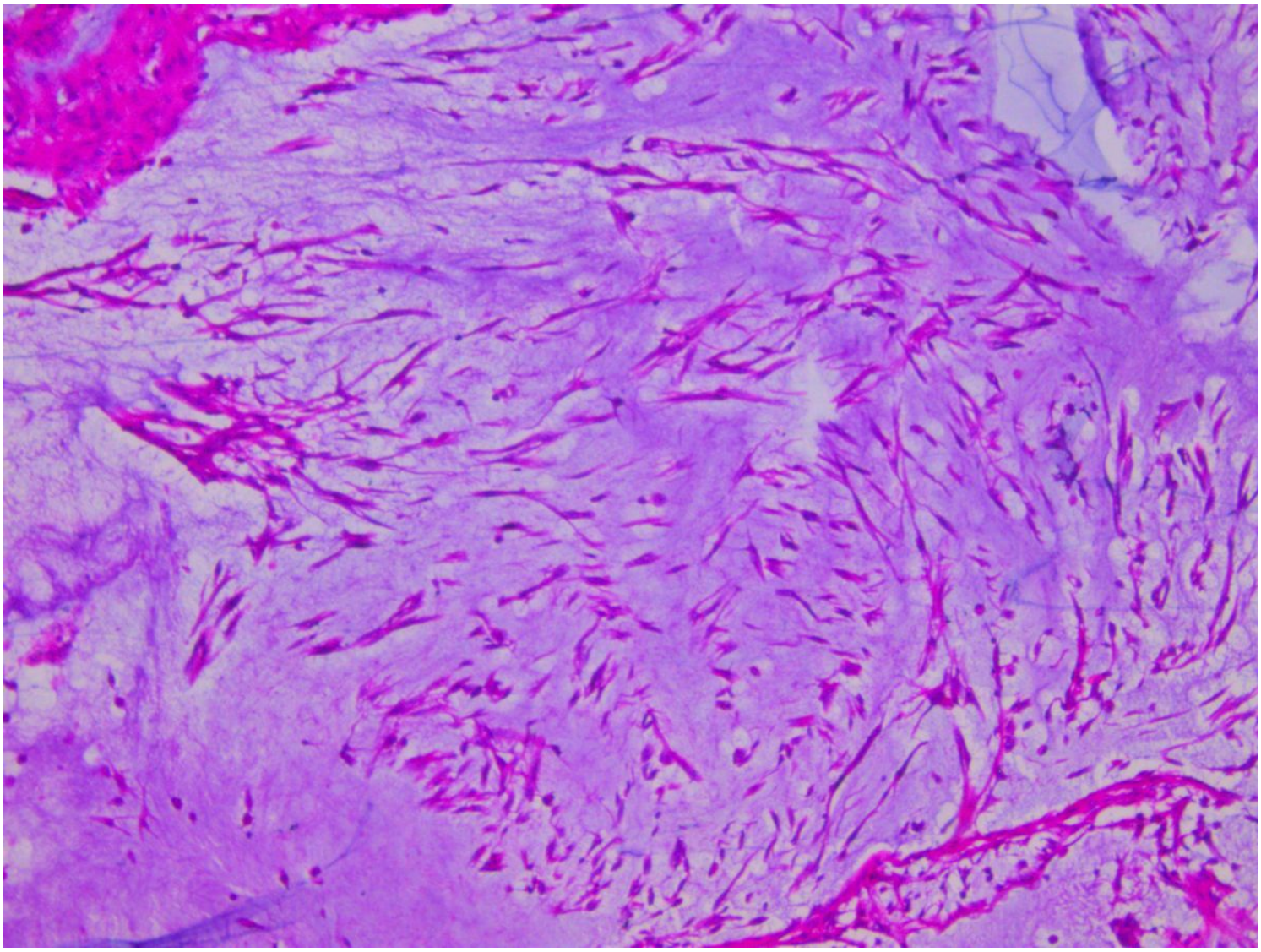

Figure 3

There is a lot of mucus here(H&E 100x).

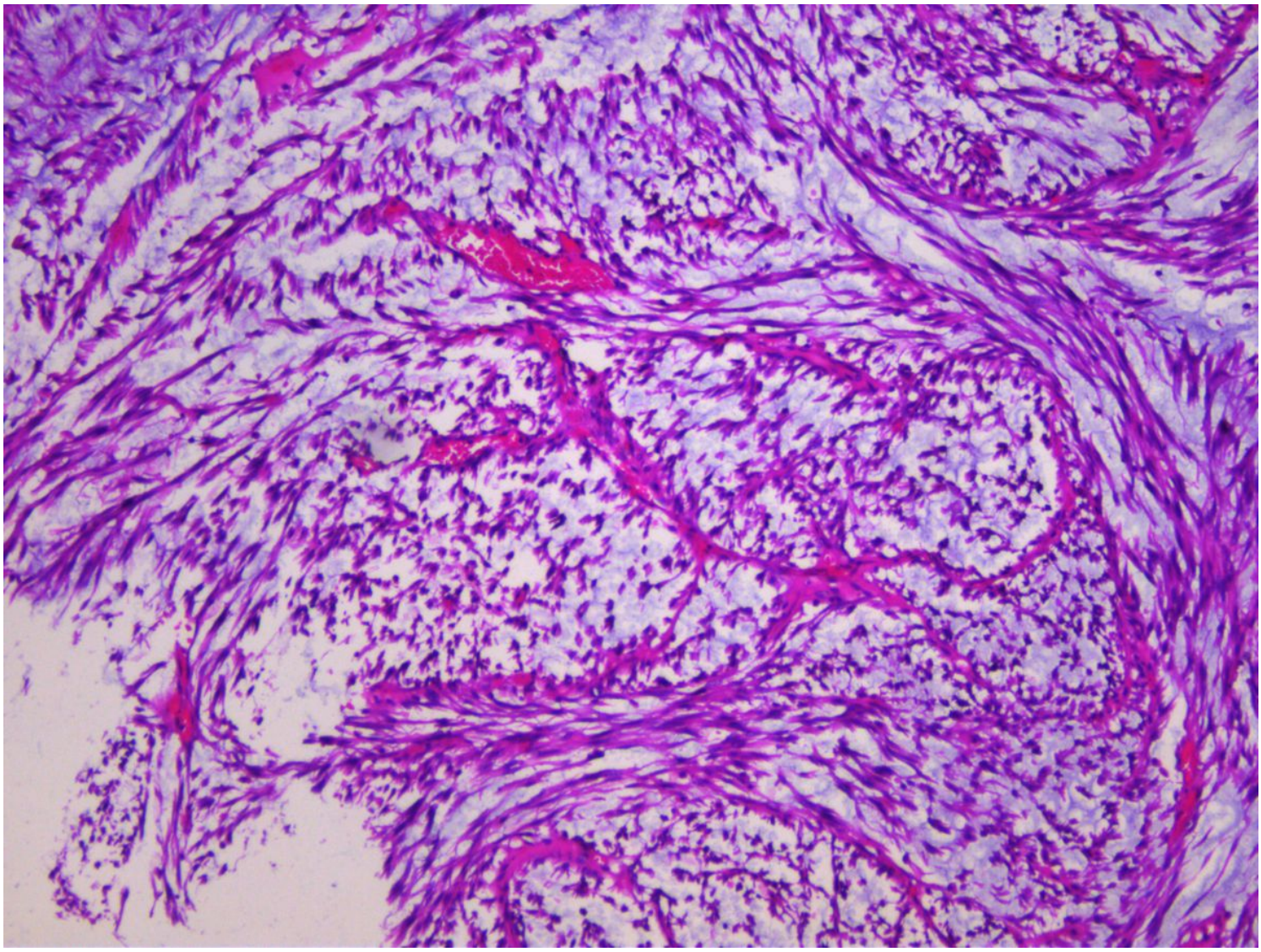

Figure 4

The tumor contained a series of short ovoids and stellate cells. The cells were attached to the reticular fibers of the myxoid stroma and arranged in filaments and cords (H&E 100x).

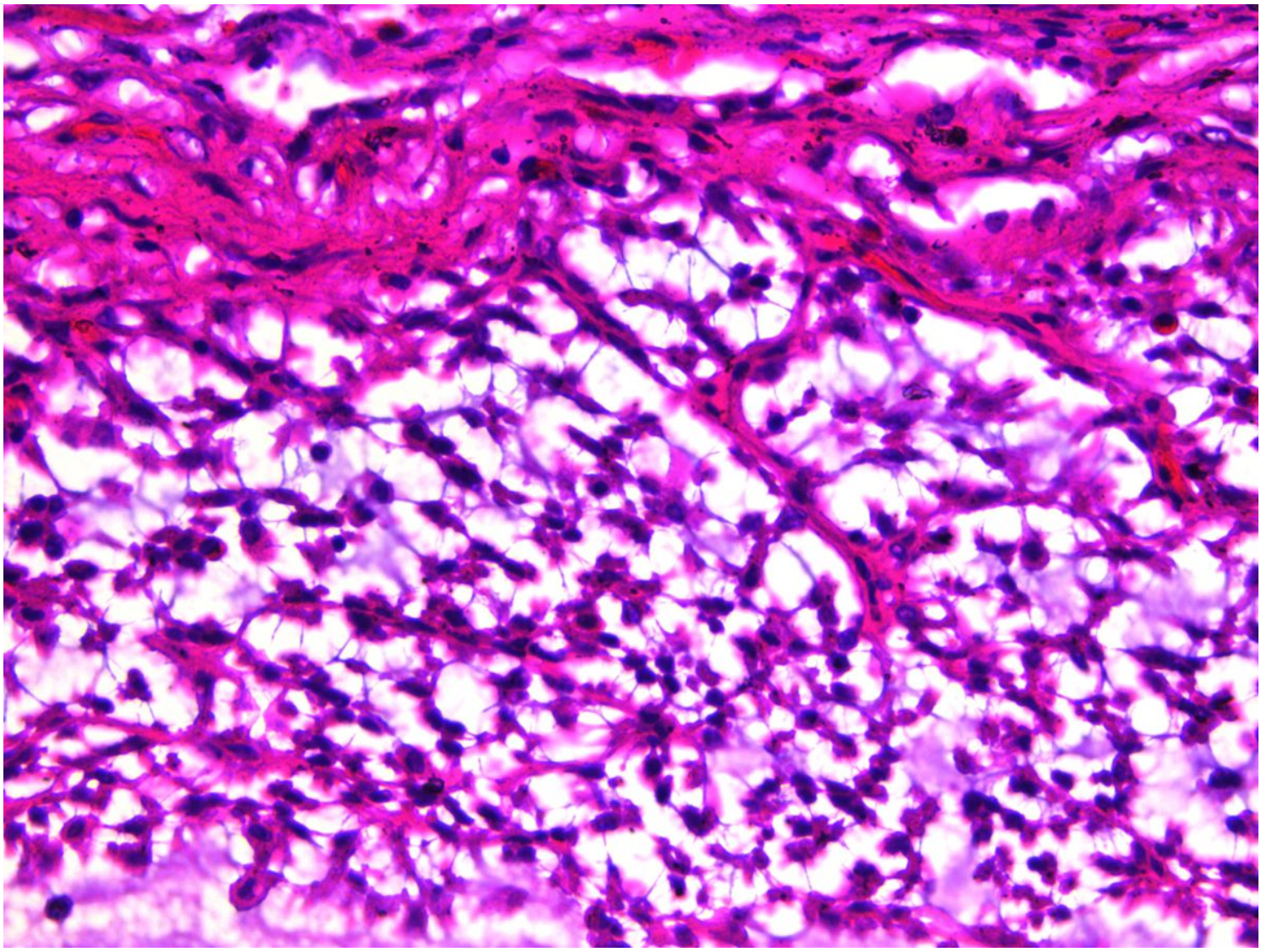

Figure 5

A large number of stellate cells and a small number of inflammatory cells the tumor cells were slightly atypia, and the large partial nuclear fission was <5/10 HFP in most regions. (H&E 400x).

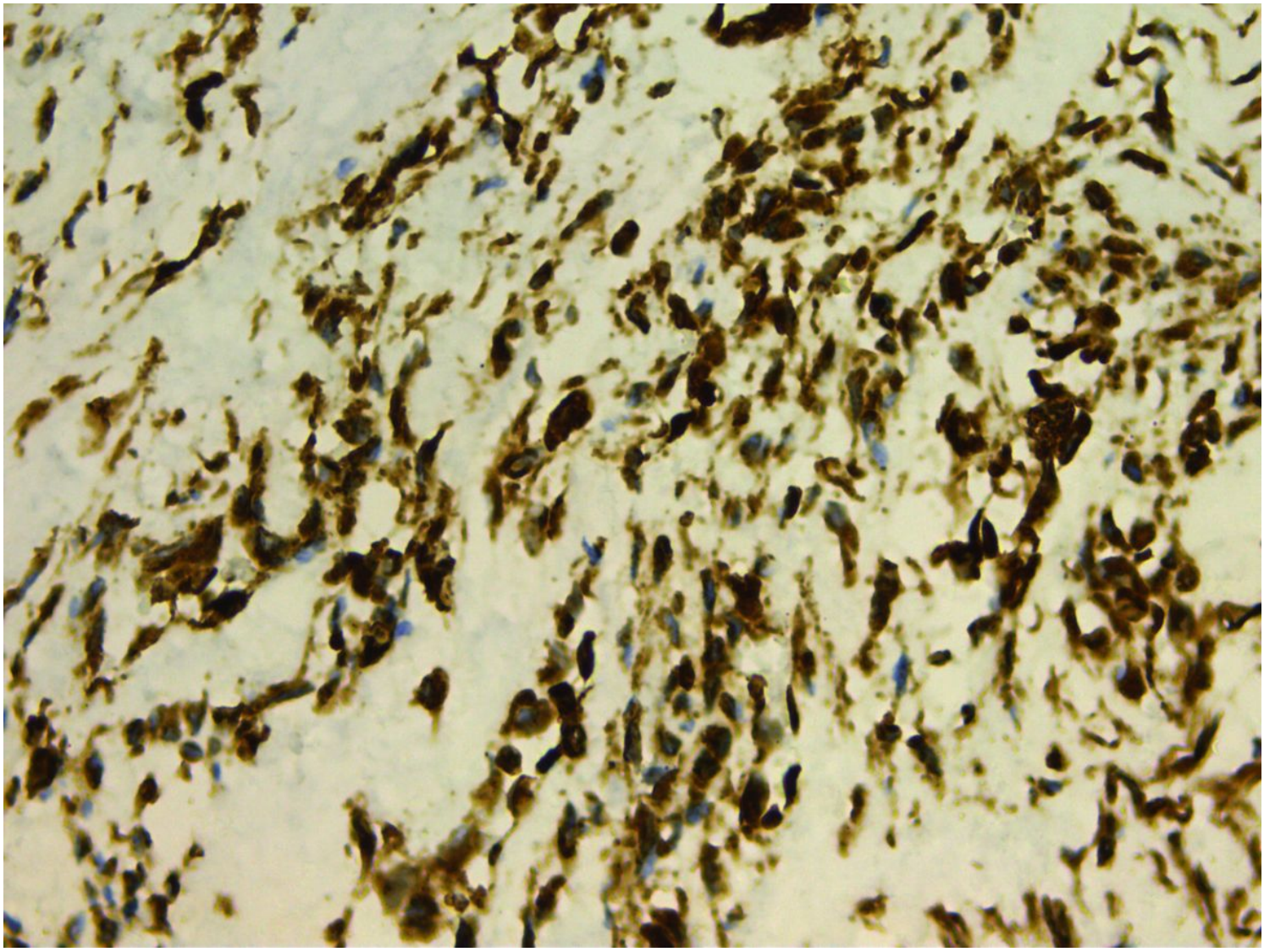

Figure 6

Immunohistochemistry staining for distinguishing antigens revealed that the tumor cells were diffusely positive for vimentin.

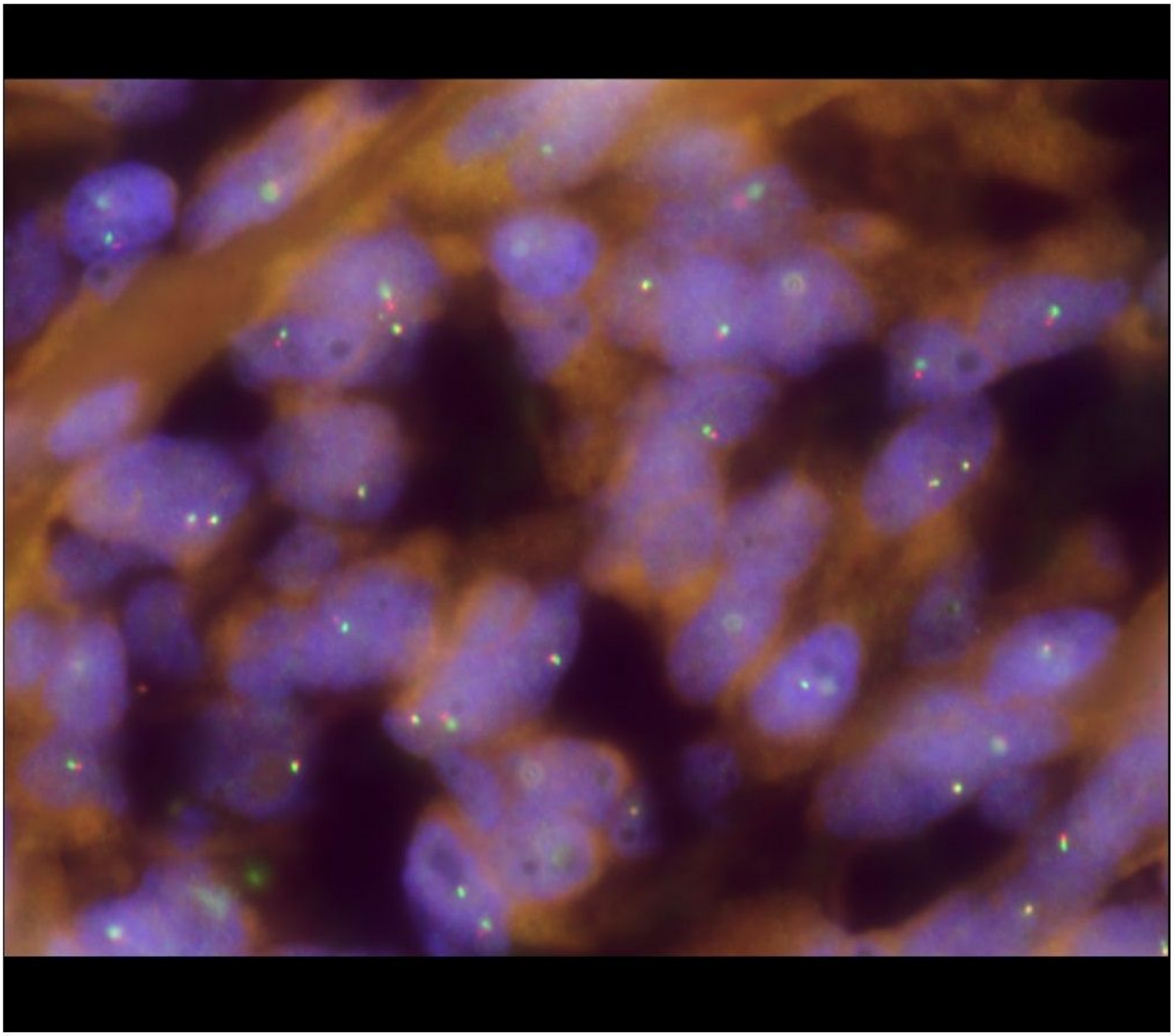

Figure 7

ALK translocation occurred because of the split red and green signals on the ALK break-apart probes.

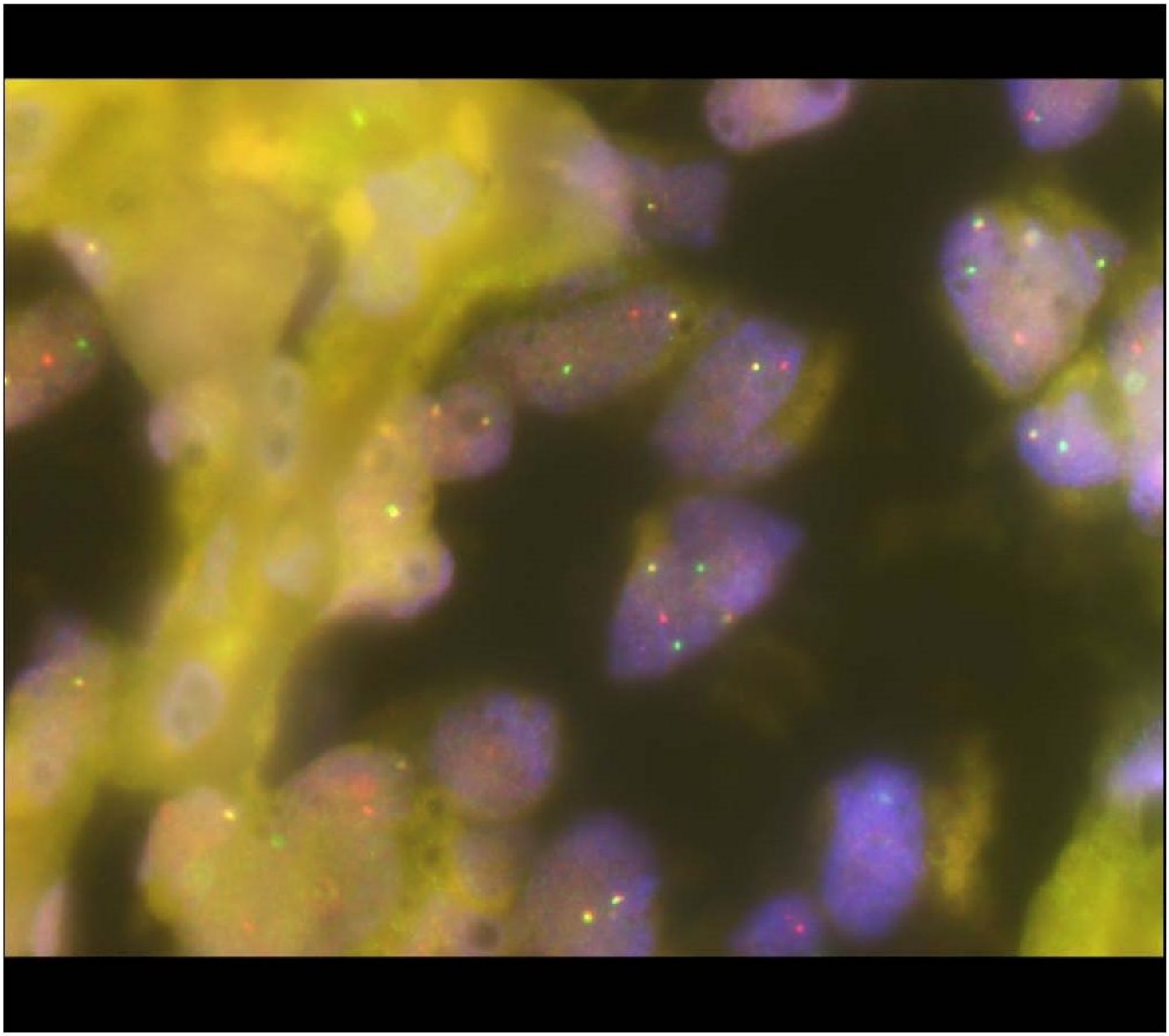

Figure 8

Red and green signal divisions were not observed on the EWSR1 separation probe.

Supplementary Files

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