Genomics Case Report

Inflammatory Myofibroblastic Tumor of the Bladder With FN1-ALK Gene Fusion: Different Response to ALK Inhibition

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Inflammatory myofibroblastic tumors are rare tumors with an ALK (anaplastic lymphoma kinase) gene rearrangement in up to 65% of all cases. In our patient, the tumor was not primary resectable due to its extension. Under neoadjuvant treatment with the first generation ALK inhibitor crizotinib no tumor response was seen, but the following therapy with the next generation ALK inhibitor lorlatinib led to a rapid and deep response, enabling a complete tumor resection by partial cystectomy. Our case indicates that ALK positive inflammatory myofibroblastic tumors which do not respond to ALK inhibition with crizotinib can be successfully treated with newer agents.   UROLOGY 146: 32−35, 2020. © 2020 Elsevier Inc.

Inflammatory myofibroblastic tumors (IMTs) are rare tumors, occurring mainly in the abdominal cavity, retroperitoneum, pelvis, lung, head and neck, and less frequently in the gastrointestinal tract, pancreas, bladder and uterus.[1,2] Children and young adults are affected most often, but IMTs may occur along the entire range of age, with a slight predominance for women.[1-5] Histologically, IMTs consist of a loosely fascicular proliferation of spindle cells with myobroblastic phenotype, variable cellularity, stromal edema and myxoid change as well as varying inflammatory infiltrate of plasma cells, lymphocytes, and eosinophilic granulocytes.[2-6] The overall recurrence rate of IMTs is about 20%, but seems much higher for abdominal and pelvic IMTs (up to 85%), and conversely lower in IMTs of the lung (<2%) and bladder (<4%).[2-4,6] Metastases (mainly in lung, brain, liver, and bone) occur in <5% of the cases.[1,2,4] In 50%-65% of all IMTs, an anaplastic lymphoma kinase (ALK) gene rearrangement can be detected, leading to a constitutive activation of the ALK tyrosine kinase, causing uncontrolled cell proliferation.[2-5] The high frequency of ALK alterations in IMTs makes it a diagnostic marker. In addition, there seem to be clinical and biological differences between ALK positive and negative IMTs: ALK positive IMTs are more frequent in females and younger patients.[4] Abdominal IMTs showed more ALK positivity than pulmonary IMTs, and ALK positive IMTs were reported to have a higher recurrence rate, whereas ALK negative IMTs were associated with a higher frequency of metastases.[2,3]

For IMTs of the urinary bladder, complete surgical resection is the targeted therapeutic strategy and the only known curative treatment. A study that reviewed 120 cases of IMTs of the bladder reported sufficient primary treatment with transurethral resection of bladder tumor (TURBT) in 60.8%, followed by partial cystectomy in 29.2% and radical cystectomy in 9.2% in cases with residual tumor.[4] With the possibility of a targeted therapy against ALK alterations with kinase inhibition, a new promising therapy option is now available.

CASE PRESENTATION

We present the case of a 43-year-old woman who suffered from dysuria and macrohematuria for 5 months. Cystoscopy showed an extensive solid and papillary tumor of the anterior wall of the urinary bladder (Fig. 1), not primary resectable by TURBT due to its large extension. CT-graphic imaging revealed an exophytic tumor with a maximum diameter of 7 cm with invasive appearance. Microscopically (Fig. 2A), extensive infiltrates of myofibroblastic proliferation were found, accompanied by numerous inflammatory cells and variable stromal myxoid and oedematous change. Several mitotic figures could be seen, without however atypical forms. There was no tumor necrosis or pleomorphy. Immunohistochemistry demonstrated diffuse expression of smooth muscle actin

Figure 1. Initial macroscopic aspect in cystoscopy. (Color version available online.)

and focal positivity for cytokeratins, while desmin, S100 and CD34 were negative (not shown), leading to the suspicion of an inflammatory myofibroblastic tumor. The immunohistochemistry for ALK1 (5A4) protein was strongly and diffusely positive (Fig. 2B).

The tumor was analyzed by next generation sequencing using the RNA based Fusion Plex Sarcoma Panel (Supplementary Table 1). We identified a Fibronectin 1 (*FN1*) - *ALK* gene fusion (Fig. 3).

A neoadjuvant therapy with the first generation ALK inhibitor crizotinib was started to reduce tumor volume and thus enabling organ sparing resection. No response was observed after 2 and 4 months of treatment. To investigate the presence of an *ALK* mutation conferring resistance to crizotinib we performed the DNA-based part of the Oncomine Focus Assay (Supplementary Table 2) on the same pretreatment tumor material with the gene fusion. No known *ALK* resistance or any other mutation or copy number variant was identified by this assay (Supplementary Table 3).

After switching the medication to the next generation ALK inhibitor lorlatinib, a rapid response with a partial remission was seen within 5 weeks (Fig. 4).

Unfortunately, the patient started to complain about shortness of breath. A chest CT showed bilateral ground glass opacities, therefore, a pneumonitis was suspected. Lorlatinib was stopped, and the patient was started on corticosteroids, leading to a rapid clinical and radiological improvement. The partial remission to lorlatinib allowed a bladder sparing operative approach. Through the following laparoscopic robot-assisted partial cystectomy, a pathologic R0-resection was achieved. Histologically, residual cells of the IMT with signs of regression were seen. During a follow-up of 12 months, we found no evidence of recurrence or metastases in cystoscopy or imaging.

DISCUSSION

Genomic rearrangements involving ALK gene fusion with about 30 different partners have been described in a broad spectrum of malignancies. They are best known in certain lymphomas and in adenocarcinomas of the lung.[7] Our case was characterized by a FN1 (Fibronectin1)-ALK gene fusion, which has been found previously in a 12-year-old male with an IMT of the bladder.[8]

In several case reports and phase 1b/phase 2 studies, responses of ALK positive IMTs to crizotinib have been shown, with an overall response rate of 50%-86%, including complete responses in 36% and partial responses in 50% of patients.[9-12] Crizotinib is therefore the standard of care for patients with unresectable ALK mutated IMT. Remarkably, the tumor of our patient did not respond to a neoadjuvant treatment with the first generation ALK inhibitor crizotinib, but reacted with a rapid and deep response to the next generation ALK inhibitor lorlatinib. To our knowledge, this is the first case of an IMT showing a differential response to distinct ALK inhibitors. It is noteworthy that a grade 3 pneumonitis developed only with the therapeutically successful tyrosine kinase inhibitor (TKI) lorlatinib, but not with crizotinib.

It is known that a resistance to first generation TKIs can occur after some months of therapy, due to development of secondary mutations or activation of bypass pathways.
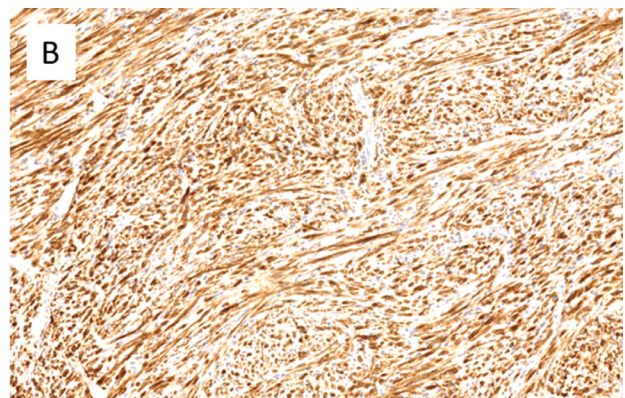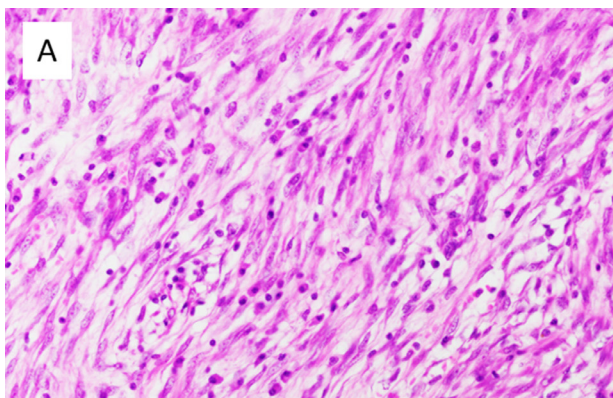

Figure 2. Histopathology of the tumor sample: (**A**) Myofibroblastic spindle cell proliferation with slightly oedematous myxoid background and inflammatory infiltrate (HE stain; original magnification 200x). (**B**) Immunohistochemistry showed diffuse and strong expression of ALK1 protein (5A4 antibody) in all tumor cells, leading to the diagnosis of an IMT (original magnification 100x). (Color version available online.)
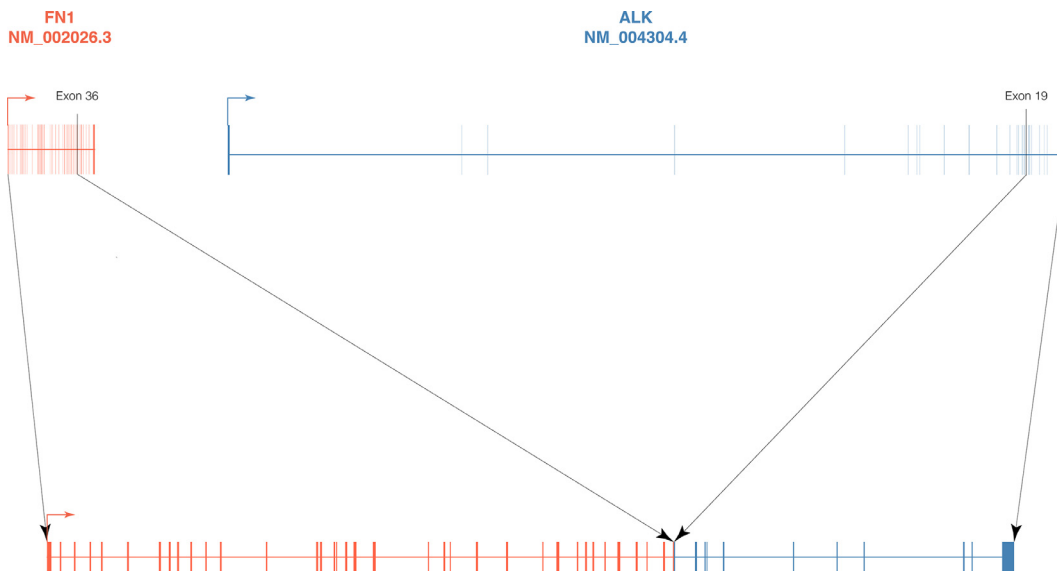
Figure 3. Schematic depiction of the gene fusion found in the tumor. Exon 36 of *FN1* (in red) fused with Exon 19 of *ALK* (in blue). The blue and red arrows show the direction of transcription. The black arrows show the 5' and 3' end of unmutated and fusion transcripts as well as the breakpoints in the unmutated and fusion points in the mutated transcripts. The fusion transcript downstream of the fusion point was in frame. (Color version available online.)

To address this problem, next generation TKIs have been developed.[13,14] Some well-known resistance mutations (missense or insertion mutations) against the first generation TKI crizotinib are L1196M, G1202R, S1206C/Y, C1156Y/T, L1152P/R, I1171T/N, F1174C/L/V, G1269A/S, V1180L, F1245C, and 1151Tins.[13-15] In our patient, none of these resistance mutations were detected (Supplementary Table 3), thus the mechanism of resistance to crizotinib remains unclear. In vitro, tumor cells expressing FN1-ALK had a significantly higher sensitivity to lorlatinib compared to crizotinib (half maximal inhibitory concentration IC50 of 35 nM vs. 153 nM, respectively).[7] It is interesting that the FN1-ALK fusion protein is the only fusion protein, which retains the transmembrane domain and has one of the highest kinase activity of all ALK fusion partners.[7] From a biochemical perspective, it is not entirely clear why different ALK fusion variants have different sensitivities to ALK TKI therapies,

because each ALK fusion protein contains the entire ALK tyrosine kinase domain and should theoretically respond to TKI. Perhaps the various ALK fusion partners have different biochemical and cellular properties and affect kinase activity, protein stability or tertiary structure, thus differentially influencing the activity of the various TKI.

Our case indicates that ALK positive IMTs, which do not respond to ALK inhibition with crizotinib, might not be refractory to ALK inhibition but can be successfully treated with newer agents. This could be of importance both in the neoadjuvant and in the palliative setting especially to prevent radical intervention and sustain bladder function.

Prospective therapeutic studies should include the determination of the involved ALK fusion partners in order to improve the knowledge about the mechanism of action and the efficacy of ALK TKIs in the treatment for IMTs.

Figure 4. (**A**) CT of the pelvis showing the tumor in the bladder (maximum diameter of 7 cm) before treatment. (**B**) Partial remission of the tumor (3.3 cm) after therapy with lorlatinib.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2020.09.026.

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