ALK Inhibition for the Treatment of Refractory Epithelioid Inflammatory Myofibroblastic Sarcoma

Mikihiro Fujiya and Yutaka Kohgo

Key words: epithelioid inflammatory myofibroblastic sarcoma, ALK inhibitor, RANBP2-ALK fusion


Inflammatory myofibroblastic tumors (IMTs) are rare mesenchymal neoplasms composed of myofibroblastic spindle cells with inflammatory infiltration, particularly of plasma cells and lymphocytes. IMTs usually arise in the lungs or abdominal soft tissue in children and young adults (1). IMTs are neoplasms thought to possess an intermediate biological potential for malignancy, although they rarely metastasize (less than 5% of tumors) (2). The tumor size, mitotic activity and presence of necrosis are not well correlated with the clinical outcome, while the proliferation of highly atypical polygonal, round or spindle cells with vesicular and/or large nuclei are findings of malignant transformation (3, 4). Clonal rearrangement of chromosome 2 at band 2p23, involving the gene encoding Anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase identified to be a component of the Nucleophosmin (NPM)-ALK fusion oncoprotein aberrantly expressed in anaplastic large cell lymphomas (ALCLs), has been reported to be detected in approximately 50% of IMTs (5, 6). Many other ALK partner genes were subsequently identified in IMTs, including tropomyosin 3 (TPM3) and tropomyosin 4 (TPM4) (7), clathrin heavy chain (CLTC) (8), Ran-binding protein 2 (RANBP2) (9), cysteinyl-tRNA synthetase (CARS) (10), 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (ATIC) (11) and SEC31L1 (12), all of which provide active promoters for the fusion gene, likely in response to NPM binding.

While the correlations between the expression of ALK and/or particular ALK partners and the prognosis of IMT remain unknown, several case reports have suggested that IMTs with fusion between ALK and RANBP2, a very large protein located at nuclear pores (13), usually exhibit an epithelioid/round cell morphology and follow a more aggressive clinical course (1, 13-15). Recently, Maríño-Enríquez et al. proposed a subclass of IMTs consisting primarily of round-to-epithelioid cells with malignant characteristics, called epithelioid inflammatory myofibroblastic sarcoma (EIMS) (16). The authors suggested that EIMS display the potential for a high rate of recurrence after surgery and are associated with a poor prognosis.

In this issue of Internal Medicine, Kurihara-Hosokawa et al. reported a case of EIMS originating from an abdominal organ in a patient with diabetes insipidus, hypothyroidism and primary adrenal insufficiency (17). The tumor was found to be a heterogeneously dyed mass that joined together in the ileum on the right side of the pelvis when viewed on contrast-enhanced computed tomography and was visualized as a half-round area of elevation on the mouth side 15 cm from the ileocecal valve using colonoscopy. At that time, the authors diagnosed the lesion as a gastrointestinal stromal tumor (GIST) and surgically removed it. During the surgery, several white nodules were observed in the mesentery of the sigmoid colon, suggesting peritoneal dissemination. The excised lesions indicated a tumor spreading from the submucosa to the muscular and subserosal layers. Meanwhile, the histological findings revealed spindle, polygonal and epithelioid atypical tumor cells with polymorphism, and figures of nuclear division were observed against a background of apparent permeation of inflammatory cells, such as neutrophils. The authors then suspected that the tumor was an EIMT and performed an immunohistological examination, which detected a rearranged ALK gene product in the nuclear membrane. Moreover, they identified the RANBP2-ALK fusion gene using reverse transcriptase polymerase chain reaction (RT-PCR) and sequencing assays, thus confirming the tumor to be an EIMT. The tumor rapidly regrew after the first and second surgeries, suggesting a high malignant potential. The lesion was subsequently treated with chemotherapy with doxorubicin, although no effect was observed. Thereafter, the patient was treated with an ALK inhibitor, crizotinib, and the tumor shrank in size.

Because EIMTs frequently contain a rearranged ALK...
ALK inhibitors are theoretically useful for treating these tumors, regardless of the site of origin. Butrynski et al. reported a case of IMT with RANBP2-ALK fusion, in which the administration of ALK inhibitor resulted in a sustained partial response (18). The accumulation of further cases of EIMTs treated with ALK inhibitors is therefore expected to contribute to the establishment of a new therapeutic strategy for EIMTs.

The authors state that they have no Conflict of Interest (COI).

References