Effectiveness of Crizotinib for Inflammatory Myofibroblastic Tumor with ALK mutation

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Abstract:
Inflammatory myofibroblastic tumor (IMT), a rare sarcoma, is primarily treated via resection of the mass. However, in cases of recurrence or unresectable tumors, no standard care exists. While crizotinib, an anaplastic lymphoma kinase (ALK) inhibitor, is only approved for non-small-cell lung cancer with ALK mutation, it is reportedly effective for other malignant tumors with ALK mutation. We herein report a case involving a 37-year-old woman with retroperitoneal IMT with ALK mutation, who experienced recurrence after complete resection, in whom crizotinib treatment resulted in complete response. ALK-inhibitor efficacy against malignancies with ALK mutations should be investigated in future.

Key words: ALK mutation, crizotinib, inflammatory myofibroblastic tumor

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tumor was composed of spindle cells in a storiform growth pattern with infiltrating inflammatory cells that were mainly composed of plasma cells (Fig. 2A). An immunohistochemical analysis revealed that the tumor cells were positive for ALK (in the cytoplasm) (Fig. 2B) and negative for S-100, desmin, c-kit, and CD34. ALK gene rearrangement was detected by fluorescent in situ hybridization (Fig. 3); thus, the tumor was diagnosed as IMT with ALK rearrangement. We performed RNA sequencing to identify the partner gene and observed that the ALK gene had multiple fusion partner genes: TPM3 (tropomyosin 3), MPRIP (myosin phosphatase Rho interacting protein), KLC1 (kinesin light chain 1), KIF5
B (kinesin family member 5B), EML4 (echinoderm microtubule associated protein like 4), and HIP1 (huntingtin interacting protein 1), in descending order from the point of the read counts. Thoracoabdominal examinations using CT were conducted every 3 months, and the first recurrence was observed 7 months after the operation (Fig. 4A). The largest mass was located between the IVC and the right kidney. Small nodal paravertebral lesions showed the uptake of fluorodeoxyglucose and a small mass between the IVC and the pancreas was detected by MRI; these were also likely to be recurrent lesions. Since the suspected recurrent lesions were multiple and unresectable, we assessed that they were inoperable. The patient, whose Eastern Cooperative Oncology Group Performance Status was 0, started crizotinib therapy at a dose of 500 mg per day. Before starting crizotinib, we obtained written informed consent from the patient for off-label use and the approval of crizotinib use in our study by the Ethics Committee of Kobe City Medical Center General Hospital. We discontinued crizotinib one month later, because the patient’s aspartate transaminase (AST) and alanine transaminase (ALT) levels increased to 47 U/L and 112 U/L, respectively. Two weeks later, her liver enzymes recovered to within normal limits, and crizotinib therapy was restarted at a dose of 250 mg/day, which was increased to 400 mg/day three weeks later. ALT transiently increased to 73 U/L but finally reached within normal limits. The patient experienced grade 1 visual disturbance (afterimage) and grade 1 diarrhea; however, they were tolerable. Positron emission tomography-CT revealed that she had achieved a complete response (Fig. 4B); thus, we discontinued crizotinib. The total administration period was five months. Local recurrence was observed again at nine months after treatment, at the same location as the first recurrence (Fig. 4C). This time the mass was small, and she underwent surgical resection. ALK staining of the resected tumor was positive. The patient is now free from any treatment and is receiving regular imaging surveillance.

Discussion

IMT is a rare mesenchymal tumor with an unclear etiology. It can arise in various locations, and is locally aggressive. The first choice of treatment for IMT is surgical resection. Local recurrence may occur once or more than once, but distant metastasis is rare (1). Approximately 50% of IMTs harbor ALK gene rearrangement with various fusion partner genes (2). It is known that the pathological features of IMTs, such as the mitotic rate, presence or absence of necrosis, or cellular atypia, do not correspond with the clinical outcome (3, 4). On the other hand, ALK rearrangement has been associated with local recurrence but not with distant metastasis, according to a previously reported immunohistochemical study of IMTs (4). ALK immunostaining is categorized into three patterns, which appear to be determined by fusion partners (3). The three staining patterns are as follows: smooth cytoplasmic staining, granular cytoplasmic staining, and distinctive nuclear membrane staining; our case showed smooth cytoplasmic staining, which is reason-
Calcium is an important electrolyte in the body, and its homeostasis is crucial for various physiological functions, including muscle contractions, nerve impulse transmission, and blood clotting. Calcium is primarily found in bones and teeth, where it is stored in the form of hydroxyapatite. The balance of calcium in the blood is maintained by the parathyroid glands, which release parathyroid hormone (PTH) in response to low blood calcium levels. PTH stimulates the release of calcium from the bones and increases calcium absorption from the intestine. On the other hand, calcitonin, secreted by the thyroid gland, plays a role in reducing blood calcium levels by inhibiting bone resorption.

Calcium homeostasis is also regulated by vitamin D. Vitamin D, produced in the skin upon exposure to ultraviolet light, is converted in the liver to 25-hydroxyvitamin D, which is then further converted in the kidneys to 1,25-dihydroxyvitamin D (calcitriol). Calcitriol binds to vitamin D receptors located in the kidneys, intestine, and bone, increasing calcium absorption from the diet and stimulating the conversion of bone to plasma calcium.

In disorders such as hyperparathyroidism, the parathyroid glands secrete excessive amounts of PTH, leading to increased bone resorption and hypercalcemia. Conversely, in hypocalcemia, the parathyroid glands do not secrete enough PTH, resulting in decreased bone resorption and reduced plasma calcium levels. These disorders can be diagnosed through laboratory tests that measure blood calcium and PTH levels. The treatment of hyperparathyroidism involves surgical removal of the overactive parathyroid glands, while hypocalcemia is managed with calcium and vitamin D supplements.

In conclusion, calcium homeostasis is a complex process involving multiple factors, including the parathyroid glands, the thyroid gland, and vitamin D. Understanding these processes can help in the diagnosis and management of disorders related to calcium imbalance.