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Anaplastic lymphoma kinase inhibitor-associated myositis

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Anaplastic lymphoma kinase (ALK) inhibitors have been used in patients with non-small cell lung cancer (NSCLC) harboring *EML4-ALK* fusion gene.[1] Severe skeletal muscle adverse events of ALK inhibitors, such as muscle weakness, have seldom been reported.[2,3] Herein, we describe a patient who showed a severe skeletal muscle deficit after the administration of the ALK inhibitor, alectinib, and was successfully treated by corticosteroids without withdrawal from the cancer therapy.

Case report

A 55-year-old woman was diagnosed with stage IV (cT1 cN pM1c) lung adenocarcinoma harboring *EML4-ALK* translocation, which was confirmed by the fluorescent in situ hybridization analysis. Metastases in brain, liver, and kidney were found at the time of primary diagnosis. She first received crizotinib for 1 month but showed resistance to it. Therefore, it was replaced by alectinib (600 mg/d) combined with whole brain radiation therapy (30 Gy). The treatment led to regression of the tumors, maintaining her good general status. However, 7 months after change of the treatment, she presented slowly progressive weakness of axial and proximal muscles and mild posterior neck pain. On examination, she showed head drop and could not raise her arms above her head nor stand up from a squatting position. Neurologic examination revealed no further abnormal signs of muscle bulk, cranial nerves (in particular, no ptosis), cerebellar, sensory, and autonomic systems. Serum creatine kinase (CK) levels were elevated to 1342 U/L (normal: <171). Myositis-specific/associated autoantibodies were negative as far as tested: SRP, TIF1γ, Mi-2, Jo-1, cN1A, RNP, Sm, Ro/SS-A, LA/SS-B, and Scl-70. Antinuclear antibodies (MPO and PR3) and paraneoplastic and myasthenic autoantibodies were also not detected: Hu, Yo, Ri, CV2, amphiphysin, recoverin, SOX1, Ma2, titin, acetylcholine receptor, MuSK, VGCC (N and PQ), and MAG. M protein was not detectable in her serum. Tumor enlargement or tumor marker elevation was not observed. Skeletal muscle MRI showed edematous changes in the posterior neck muscles, which were enhanced by gadolinium (figure, A–E). EMG demonstrated myopathic changes with fibrillation potentials and positive sharp waves in cervical paraspinal muscles. A repetitive nerve stimulation test was normal. There were no abnormal findings in cardiac and respiratory tests. Biopsy of left semispinalis capitis muscle was performed, revealing overt inflammatory changes with marked fibrosis (figure, F–M). Many fibers were atrophic and showed overexpression of major histocompatibility complex class I. A few necrotic fibers were observed. Inflammatory cells were diffusely present and formed several clusters consisting of predominantly CD20-positive cells. Sarcolemmal C5b-9 complement deposition on non-necrotic fibers was scattered. Because inflammatory myopathy was shown, corticosteroid treatment was started (150 mg/d [~2 mg/kg body weight/day] with prednisolone for 3 days, followed by 80 mg/d and gradually tapered to 7 mg/d for 2 months). The treatment was effective, leading to recovery of head drop and relief of neck pain within 2 weeks and

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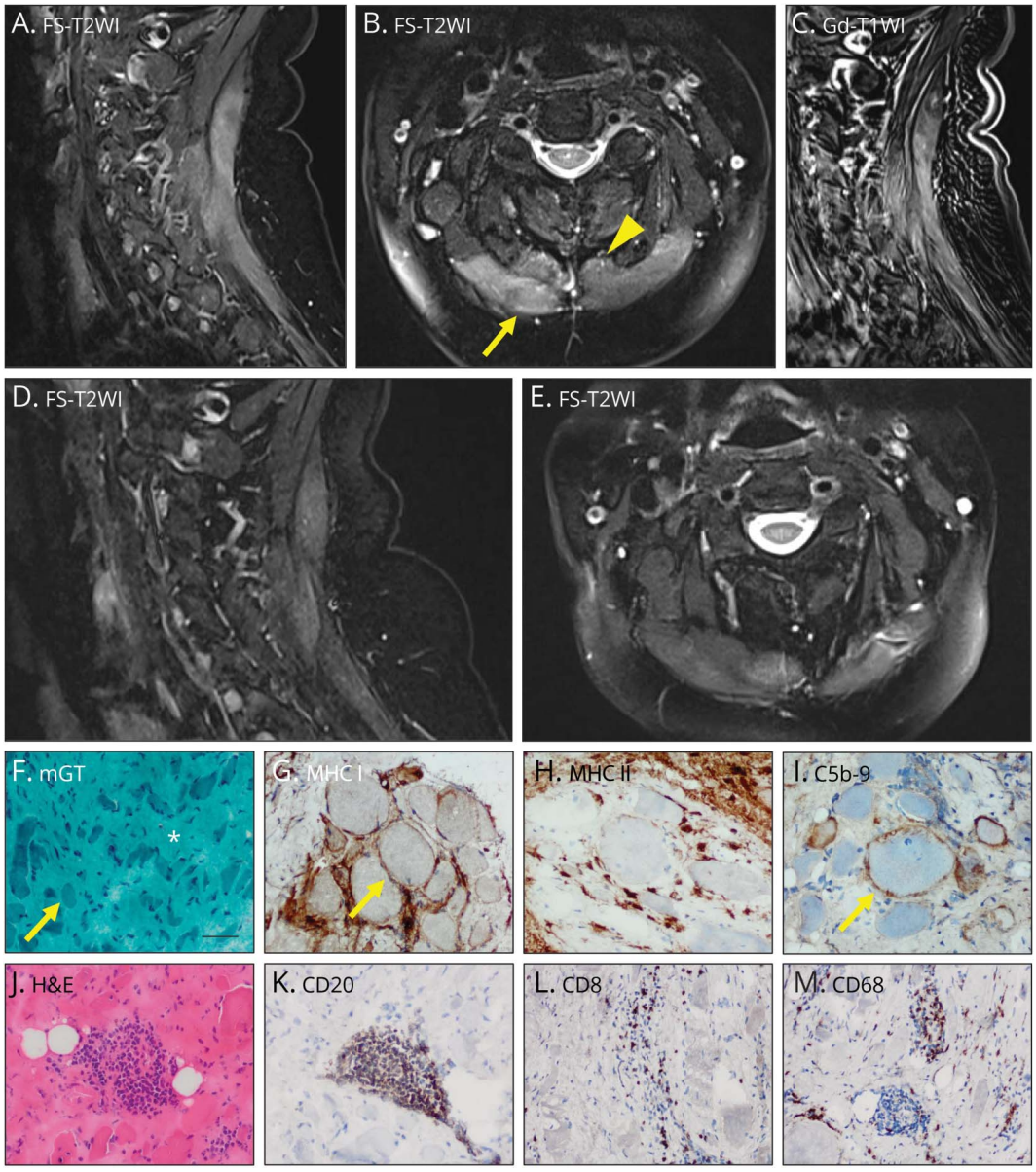
normalization of muscle power in 4 limbs within a few weeks. Two months after the initiation of corticosteroid treatment, serum CK levels were decreased to 272–341 U/L. Eventually, under corticosteroids, the patient tolerated continuation of cancer therapy well.

Ethical statement

Informed consent was obtained from the patient. The Charité Ethics Committee (EA2/163/17) granted ethical approval.

Figure MRI and pathology of skeletal muscles



(A–E) 3 T MRI of the cervical spine. Upper row shows the initial status at presentation (A–C): marked bilateral muscular edema was observed in trapezius, splenius (arrow), and semispinalis (arrowhead) muscles in sagittal and axial fat-suppressed T2-weighted imaging (A and B: FS-T2WI). IV contrast administration shows vivid enhancement in the same region in sagittal subtracted T1-weighted imaging (C: Gd-T1WI). These findings are suggestive of inflammation of the muscles. Lower row shows improvement of the inflammatory change 7 weeks after initiation of corticosteroid treatment in sagittal and axial FS-T2WI (D and E). (F–M) Pathology of the biopsied semispinalis capitis muscle. Most fibers are atrophic, and marked endomysial fibrosis is present (F: modified Gömöri trichrome stain [mGT]. The arrow and the asterisk indicate a myofiber and fibrous tissue, respectively. Bar: 50 μm). Overexpression of major histocompatibility complex class I is observed on sarcolemma of many fibers (arrow), whereas major histocompatibility complex class II is not overexpressed on myofibers (G and H: immunohistochemistry for major histocompatibility complex classes I and II [MHC I and II]). Myofibers showing C5b-9 complement deposition predominantly on sarcolemma of non-necrotic fibers (arrow) are scattered in <3% of the total number of myofibers (I: immunohistochemistry for C5b-9 complements [membrane attack complex]). There are several clusters of mononuclear cells, which consist of predominantly CD20-positive cells (J: hematoxylin and eosin stain [H&E]. K: immunohistochemistry for CD20). Focal infiltration of CD8− (L) or CD68− (M) positive cells are observed both in perimysium and endomysium, immunohistochemically. These staining results argue in favor of a B-cell mediated process, likely to interfere with the interferon-mediated pathways, accompanied by a solid T-cell response within the tissue as well.

Discussion

This patient with advanced NSCLC had developed severe proximal and axial muscle weakness after ALK inhibition therapy, characteristically showing head drop. The agents included alectinib and crizotinib, but, considering the clinical course, alectinib was more likely responsible for the onset of symptoms. According to the reports of the Food and Drug Administration in the United States, severe (grade 3, based on the Common Terminology Criteria for Adverse Events) myalgia or musculoskeletal pain and CK elevation occurred in 1.2% and 4.6%, respectively, of patients treated with alectinib.[4] For crizotinib, there was no description of severe myalgia or any level of CK elevation.[5] A report regarding sequential therapy with crizotinib followed by alectinib did not mention any muscular adverse event.[3] Severe adverse muscular events causing obvious muscle weakness are rare, but still, the present case raises the possibility that ALK inhibitors, especially alectinib, can cause it. The etiology of the muscle weakness is inflammatory as shown by myopathological analysis and good response to corticosteroid therapy. It should be noted that the muscle affection was so responsive to corticosteroids that the patient could tolerate the cancer therapy and thereby kept her daily activity level. The clinical presentation of this case is partially similar to what has been described in myositis as an immune-related adverse event due to PD-1 immune checkpoint inhibitors (e.g., head drop and efficacy of corticosteroids).[6,7] Increased fibrotic tissue was striking, which may be due to the nature of paraspinal muscles and enhanced by radiotherapy.

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Disclosure

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