Inclusion Body Myositis Triggerred with Long-term Imatinib Use

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Abstract

Inclusion body myositis (IBM) is an acquired myopathy of both inflammatory and degenerative nature. Here we report a case of IBM associated with prolonged use of imatinib not reported in the literature so far. An 81 years old male with a history of gastrointestinal stromal tumor (GIST) operated 8 years ago was evaluated for the progressive loss of weight and muscle strength leading to total immobilization in 6 months. He was under imatinib for 8 years despite the remission of GIST. Physical examination disclosed diffuse loss of muscle strength, most prominently involvement of distal upper and proximal lower extremity in an asymmetrical pattern with normal serum creatinine kinase level (CK). Further investigations including bilateral thigh MRI, electromyography (EMG), and PET/CT suggested myositis and degenerative myopathy and ruled out any malignancy. Quadriceps femoris biopsy proved the diagnosis of IBM and no trigger except for imatinib was displayed. Clinical improvement in terms of wieght loss and muscle weakness was achieved after discontinuation of imatinib. Since imatinib is widely used in different conditions, it is important to be aware of even its rare adverse effects. Poor response of IBM to conventional immunosuppressive agents enhances the value of etiology identification to relieve symptoms in addition to supportive care.

INTRODUCTION

Inclusion body myositis (IBM) is an acquired myopathy of both inflammatory and degenerative nature with an increased incidence in elderly and male patients. It is a rare condition with an unclear etiology, occurring with neurodegenerative findings in addition to a cytotoxic T cell-mediated immune response (1). Although several factors have been associated with the development of IBM, tyrosine kinase inhibitors seems safer in that issue and only one case of IBM developed after the use of dasatinib has been reported so far (2). Here, we report a case of IBM, associated with the prolonged use of imatinib which is the first case in literature.

CASE REPORT

An 81 years old male with the history of dilated cardiomyopathy and congestive heart failure and an operated gastrointestinal stromal tumor (GIST) of stomach 8 years ago was admitted due to urinary tract infection. He had progressive loss of weight of approximately 50 pounds and muscle strength in the last 6 months and was completely immobile for the last four months. On physical examination, he was left-handed, grip impairment and diffuse loss of muscle strength on extremities prominently at distal of right upper limb and proximal of lower limbs as 3/5 without any rash, arthritis, and organomegaly were seen. Owing his comorbidities, he was under dabigatran, furosemide, bisoprolol, and 400 mg/day of imatinib for the last 8 years. The patient declared that he gave up routine oncologist follow-up for 5 years and continued to take imatinib only. Laboratory showed hemoglobin 9.9 gr/dl, white blood cells 11800 10^9cell/L, neutrophils 9900 10^9cell/L, CRP 167 mg/L, creatinine 1.4 mg/dL, albumin 2.9 gr/dL, and pyuria on urine analysis. Liver enzymes, thyroid function tests, and coagulation parameters were normal. After antibiotherapy, acute phase reactants returned to normal range.

Owing to systemic symptoms and progressive muscle weakness; serologic tests including anti-nuclear antibody (ANA), extractable nuclear antigen (ENA) panel, anti-jo1 antibody, and serum creatine kinase (CK) levels were requested and found in normal range. In bilateral thigh MRI both acute and chronic findngs of muscle damage were observed. Figure 1 a and b shows signal changes consistent with focal myositis were observed in the bilateral quadriceps femoris muscles, especially in vastus medialis muscles with right side dominance, and atrophic fatty degeneration in the distal musculotendinous junction of the semimembranosus muscle most prominently. Both muscle atrophy and asymmetric fatty infiltrations suggesting chronic changes, and hyperintensity on T2-weighted fat-suppressed images suggesting acute myositis with normal levels of CK were consistent with IBM.

Electromyography revealed sural and supperoneal sensory unresponsiveness, prolongation in the distal latency of the median response on the right in sensory, while long distal latency and low amplitude of the median, ulnar and tibial responses, and peroneal unresponsiveness on the right were observed in motor nerve conduction studies. In the needle EMG examination, short-term, polyphasic, low-amplitude motor unit action potentials (MUAPs) and early participation patterns were observed in right deltoid, biceps, first distal interosseus, vastus medialis, and iliopsoas muscles and bilateral tibialis anterior and gastrocnemius muscles. All were interpreted as diffuse myogenic involvement in both neurogenic and myopathic manner.

PET/CT was performed to evaluate any recurrence or metastasis of GIST and exclude paraneoplastic causes and revealed physiological FDG uptake except for chronic inflammation due to remitting epididymoorchitis in the right testis. Urological evaluation, upper gastrointestinal gastroscopy, and colonoscopy were benign with no findings of relapsed GIST.

Biopsy taken from the right quadriceps femoris muscle revealed type 2 atrophy with fatty replacement, diffuse degeneration-regeneration, red-rimmed vacuoles, ragged red fibers indicating mitochondrial abnormality, and focal MHC-I positivity on muscle tissue with inflammatory cell infiltration but not vasculitis and found to be compatible with IBM (Figure 2 a, b, c, and d).

Imatinib was discontinued because there was no indication of use with proven disease remission and no other suspicious reason or malignancy was detected for IBM development. The absence of dysphagia and resistive infection led us to follow-up him without IvIg administration. One month after imatinib cessation, he was able to sit in bed and his weight was stable. In the fourth month, his weight gain was evident, and both general health status and muscle weakness were improved. At his last examination, grip impairment was resolved and MRC grades of both upper and lower limbs were 4-5/5. He became more independent and mobile in bed, started to eat own his own. Since no benefit was expected from immunosuppressive therapy; nutritional support, physical therapy and rehabilitation were given with periodic dysphagia evaluation and concurrent neurology follow-up.

DISCUSSION

In that case report, we described a case of IBM induced with long-term imatinib use. Because IBM is a rarer type of muscle pathology, identification of IBM and differential diagnosis is important. Involvement of distal upper and proximal lower extremity, asymmetrical involvement with both inflammatory and degenerative patterns in EMG, older age of patient, normal level of CK enzyme, and absence of malignancy are important clues for IBM (1, 3). Focally increased signal on fat-saturated gadolinum enhanced T1-weighted images in quadriceps femoris muscle group sparing of rectus femoris and biopsy including degenerative changes, mitochondrial abnormality, ragged red fibers and red vacuoles in addition to inflammation and MHC-1 positivity are pathognomonic and used in differentiation from other myositis groups (4). Conventional immunosuppresive agents are ineffective in the management of IBM and both dysphagia and immobilization are main major complications leading to subsequent morbidity and mortality (5).

Tyrosine kinase inhibitors have been related to several adverse effects except for myopathy or myositis (2, 6). To the best of our knowledge, this is the first case of imatinib induced IBM. In our patient, improvement of symptoms after cessation of imatinib, confirmed the trigger of IBM and found out the value of etiology identification to relieve symptoms in addition to supportive care. This is unclear whether muscle injury

developed due to prolonged use or the directly molecular property of imatinib. However, considering the much longer use of imatinib in other indications, especially chronic myeloid leukemia, duration does not appear to be the only reason. In our opinion, the main mechanism underlying this unexpected side-effect might be related with the blockage of tyrosine kinase pathway beyond the intended treatment period in disease remission which triggers a differrent response rather than the continous prolonged suppresion of bcr-abl kinase-related protein phosphorylation in myeloid cells. However, considering the wide use of imatinib in daily practise with a quite safe profile, it is important to aware of this rare adverse effect to recognize, monitorize and manage patients more effectively.

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Figure legend

Figure 1. (a) and (b). Myositis, muscle atrophy and fatty infiltration in quadriceps muscles before and after treatment, respectively, in fat saturated gadolinium enhanced T1-weighted axial plane, (c) and (d). T2-weighted fat-suppressed plane before and after treatment, respectively.

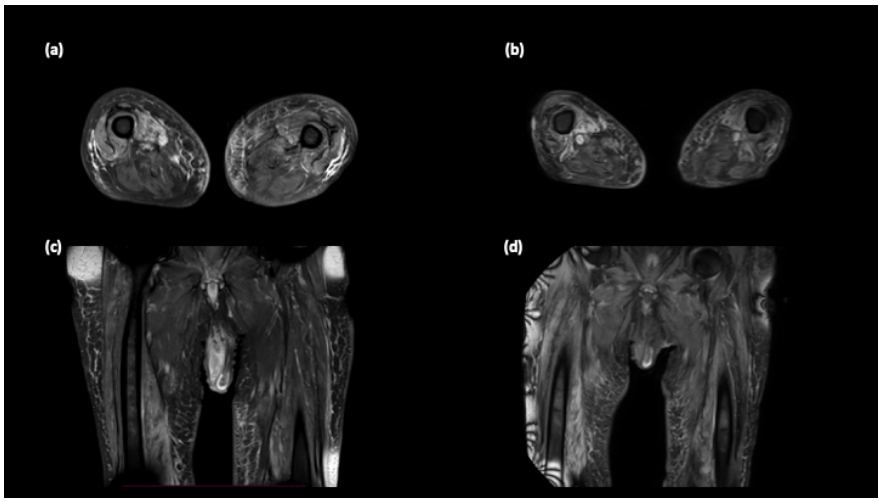

Figure 2. (a). Ragged red fibers, type 2 atrophy related angulary atrophic fibers. (b). Degenerated and regenerated muscle fibers. (c). MHC I focal positivity. (d). Type 2 atrophy with fatty replacement.

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