Acute Myopathy in a Patient with Lung Adenocarcinoma Treated with Gemcitabine and Docetaxel

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Abstract. An extremely rare case of acute inflammatory myopathy during combination chemotherapy with gemcitabine and docetaxel for advanced non-small cell lung cancer in a 57-year-old diabetic male patient is reported. Despite the early clinical partial response of the underlying malignancy to the chemotherapeutic regimen, the patient developed symmetrical, painful, proximal muscle weakness in the lower limbs with peripheral edema after the administration of the fourth cycle of treatment. The syndrome regressed definitely after the discontinuation of chemotherapy and the administration of corticosteroids. The diagnosis of drug-induced myositis is supported after the exclusion of other possible diagnoses.

Gemcitabine-induced myopathy is extremely rare, whereas peripheral edema is a well-described adverse effect of both gemcitabine and docetaxel. This is a case report of a patient with non-small cell lung cancer (NSCLC) presenting with myositis and edema in the lower limbs while on treatment with gemcitabine and docetaxel, despite the initial response of the underlying malignancy to the chemotherapeutic regimen.

Case Report

A 57-year-old male patient was referred to our clinic for stage IIIb (T4 N2 M0) NSCLC that had been diagnosed a month previously. He had already undergone an open biopsy for a peripheral pulmonary mass, revealing a moderately-differentiated lung adenocarcinoma. On his first visit, the ECOG-performance status was estimated at level 2; the patient complained of exertional dyspnea, dry cough and pleuritic chest pain over the right hemithorax. His past medical history included long-standing type 2 diabetes mellitus and hypertension, both well-regulated with felodipine and insulin, respectively. Re-evaluation for disease extent showed disease progression with ipsilateral malignant pleural effusion.

In view of the above, the patient received combination chemotherapy consisting of gemcitabine (GC) 1100 mg/m² on days 1 and 8 and docetaxel (DT) 100 mg/m² on day 8 of each 21-day cycle. A substantial symptomatic improvement was already evident after the first cycle of treatment while reassessment, including CT scan, performed after the completion of three cycles of chemotherapy, showed a clinical partial response. No significant side-effects had been noted at that stage. Therefore, an additional series of three cycles was planned. However, a week after the administration of the fourth cycle, the patient presented with rapidly evolving, symmetric proximal muscle weakness of the pelvic girdle along with bilateral lower limb myalgias mainly affecting the thighs. He did not complain of joint pain or pigmentation. On physical examination, the patient was afebrile. There was bilateral lower extremity edema without any skin lesions. Neurological examination did not disclose any sensory deficits, while deep tendon reflexes were normal. Neither fasciculations nor muscle wasting were noted. Examination of the joints was unrevealing. Muscle weakness was symmetrically present in both legs during active movements against resistance and was more prominent in the hip and knee flexors. Muscle tenderness was exacerbated by palpation over both legs.

An acute myositis was suspected and investigation revealed increased serum levels of creatinine phosphokinase, lactate dehydrogenase and aldolase (two times the upper normal limit), without laboratory evidence of acute rhabdomyolysis. Complete blood count showed mild normocytic, normochromic anemia (Hct: 37%, Hb: 12g/dL). The C-reactive protein and erythrocyte sedimentation rate were abnormally high (10 mg/dL [normal<0.8 mg/dL] and 60 mm/h, respectively), but serum autoantibodies such as rheumatoid factor, antinuclear (ANA) and anti-dsDNA antibodies were undetectable. Since the clinical presentation along with standard laboratory screen was consistent with myopathy, further investigation including electromyography/ nerve conduction studies and muscle biopsy was not attempted.
As a drug-induced myositis was considered very likely, chemotherapy was discontinued, despite the confirmed remission of the disease. A course of anti-inflammatory treatment consisting of methylprednisolone (24 mg/day) combined with diuretics (frusemide/amiloride) was initiated per os, along with prophylactic measures for diabetes and hypertension deregulation. In the following four weeks, the muscle symptoms and peripheral edema progressively disappeared, while enzymes returned to normal, allowing for tapering of methylprednisolone without rebound of myositis. Despite the temporary development of a few Cushingoid features, there were no signs of steroid-myopathy overmasking the complete muscle strength recovery. In the meantime, the patient received chest radiotherapy (40 Gy in 2 Gy fractions over 4 weeks) without significant side-effects.

**Discussion**

The case of a lung cancer patient with acute inflammatory myopathy and peripheral edema following GC/DT combination chemotherapy, despite the disease remission, is reported. The syndrome regressed after the chemotherapy was discontinued and a typical corticosteroid regimen was administered. The clinical presentation and course, as well as standard laboratory studies, supported the diagnosis of a toxic myositis, secondary to the administration of either gemcitabine or docetaxel. Differential diagnosis included paraneoplastic syndromes such as polymyositis, necrotizing myopathy and peripheral nerve vasculitis, a sensorimotor polyneuropathy and, finally, diabetic amyotrophy.

Dermatomyositis and less frequently polymyositis have been related to various malignancies including lung cancer, but both tend to precede the diagnosis or develop concomitantly with the early stages of the latter. Symmetric, proximal muscle weakness of both the upper and lower limbs along with elevated serum muscle enzymes are the prominent diagnostic features, whereas myalgias and muscle tenderness are noted in less than 50% of cases; the onset is typically subacute. In addition, dermatomyositis exhibits characteristic skin lesions (1).

Acute necrotizing myopathy is a rare paraneoplastic entity developing in the setting of metastatic malignancies including lung cancer, with clinical and laboratory features very similar to those of the previously described syndromes, except that muscle pain is much more prominent and histopathological examination identifies the presence of myonecrosis without inflammation (2).

Paraneoplastic peripheral nerve vasculitis usually precedes the detection of various malignancies including lung cancer (usually small cell). Although it typically presents with painful muscle weakness, sensory defects are also evident and the distribution of clinical manifestations is rather distal and asymmetric. Serum levels of the muscle enzymes are within normal (3).

The diagnosis of all the above paraneoplastic syndromes is primarily clinical. Since their course and evolution would be expected to be on a parallel with the underlying malignancy, the diagnosis of all three seemed unlikely in our case (4,5).

Polyneuropathy should always be taken into consideration in any patient older than 50 years of age, presenting with symmetric muscle pain in at least two of the following body regions: neck, torso, upper arms or thighs, along with elevated ESR (=40 mm/h). It represents an idiopathic synovitis of the joints of the hips and shoulders. Some patients develop peripheral swelling over the ankles and feet reflecting tenosynovitis. Nevertheless, serum muscle enzymes are not elevated. Although paraneoplastic polymyositis typically preceding cancer has also been reported, our patient did not fulfill the diagnostic criteria (6).

Sensorimotor polyneuropathy (axonal and/or demyelinating), presenting as either a paraneoplastic syndrome (mainly in lung cancer) or as a complication of cancer treatment or diabetes mellitus, initially becomes evident in the lower extremities. It manifests as symmetric muscle weakness but, in combination with sensory loss, having a rather chronic course and a distal distribution, while serum muscle enzymes are within normal. The absence of most of the above features disfavored its diagnosis in the reported case (7).

Finally, despite the longstanding glucemic control in our patient, diabetic amyotrophy (diabetic lumbar polyradiculopathy), regarded to be partially of inflammatory origin, was also taken into consideration. It typically presents with progressive proximal, painful muscle weakness in one leg, although the contralateral extremity may also become affected within days after the initial attack. Muscle enzymes are not elevated. Spontaneous recovery usually occurs over months, yet long-term deficits may remain evident. Therefore, this type of diabetic neuropathy was also precluded (8,9).

Having excluded all of the previous diagnostic possibilities on the basis of clinical criteria and standard laboratory tests, the syndrome described in our case report was attributed to the chemotherapeutic regimen.

Drug-induced myopathy is generally one of the leading causes of muscle disease and is associated with several agents. Its presentation varies from mild myalgias, with or without weakness, to massive rhabdomyolysis, dependent on the causative agent. Similarly, serum muscle enzyme concentrations range from mild to massive elevation. There are several pathogenetic mechanisms such as direct myotoxicity, immunologically-induced inflammation and indirect muscle damage, e.g. via hypocalemia or hyperthermia (10).

According to the medical literature, there are no data supporting a DT-induced myopathy. On the contrary, several case reports suggest the potential myotoxic effects of GC...
through several mechanisms. Most reports refer to radiation recall reactions following GC-based chemotherapy, resulting in myositis of the upper thorax in NSCLC patients (11). Only two cases of limb-muscle involvement associated with GC have been reported so far (12,13); in the first case, the drug caused severe extremity edema with muscle contractures, while in the second one, a GC-induced vasculitis manifested as myalgias, swelling and movement impairment in the upper and lower extremities.

Regarding the peripheral edema described in our patient, this might be attributed to a synergistic effect of the combination of DT, GC and felodipine. Fluid retention is a well-known, cumulative adverse effect of DT, sometimes occurring despite corticosteroid comedication (14,15), while edema complicates GC administration in up to 20% of cases (16,17). Although the pathogenesis remains unclear for both agents, systemic capillary protein leakage into the interstitial compartment has been proposed as the main mechanism (14-17). On the other hand, a disproportionate decrease in arteriolar resistance with subsequent increase in hydrostatic pressure in the precapillary circulation explains calcium-channel blocker-related edema, which is quite frequent (18).

Conclusion

Although the combination of gemcitabine and docetaxel is effective in NSCLC, patients receiving this regimen should be monitored for the development of a toxic myopathy syndrome. The present case report may contribute to the early recognition of a drug-induced complication that, although rare and not life-threatening, may be severely disabling, leading to the discontinuation of an otherwise successful treatment.

References


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