The cancer immunotherapy environment may confound the utility of anti-TIF-1γ in differentiating between paraneoplastic and treatment-related dermatomyositis. Report of a case and review of the literature

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With the advent of immunotherapy and with the expanding spectrum of malignancies treated with immunomodulatory agents, a new kind of adverse events has come under the spotlight. Clinicians have to be aware of immune-related adverse events and their clinical manifestations. Immunotherapy has been strongly associated with endocrinopathies, gastrointestinal, pulmonary, cutaneous, and renal toxicities but the incidence of rheumatologic adverse events is lower compared to the aforementioned systems. Dermatomyositis is an autoimmune myopathy which has been correlated to underlying evident or occult malignancies. Apart from its characteristic symptoms and signs, the presence of specific antibodies such as anti-transcriptional intermediary factor 1γ (anti-TIF 1γ) usually supports the diagnosis of paraneoplastic nature of the disease. However, a solid distinction between paraneoplastic syndrome and immune-related adverse event is still missing and remains to be elucidated. We here present a case of dermatomyositis in a male patient who underwent four cycles of combined ipilimumab and nivolumab immunotherapy. This is, to our knowledge, the first case of dermatomyositis following combined immune checkpoint inhibition therapy.

Key words: urothelial cancer, dermatomyositis, immunotherapy, ipilimumab, nivolumab, anti-TIF-1γ, paraneoplastic, autoimmune.

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Introduction

Immunotherapies have been approved for the treatment of a number of malignancies the last few years [1]. With the advent of these immunomodulating agents, the incidence of immune related adverse events increased and clinicians have to aware of these entities when introducing such therapies to their patients [2]. Endocrinopathies, gastrointestinal as well as pulmonary, renal, and neurological adverse events have been well described along with their management algorithms. However, the incidence of rheumatologic diseases is less frequent than the aforementioned, particularly the development of dermatomyositis [2].

Dermatomyositis, an idiopathic autoimmune myopathy with characteristic symptoms and signs, as well as laboratory, electromyographic, and biopsy findings, is often associated with underlying malignancies [3]. The coexistence of cancer and dermatomyositis has been investigated indicating that dermatomyositis is a possible paraneoplastic manifestation of the underlying malignancy, either evident or occult [4]. Autoantibody specificities have been related with distinct clinical subsets of dermatomyositis and may help for diagnosing an associated cancer [5, 6].

We here present a case of a patient with no history of autoimmune disease, who developed dermatomyositis after completing four cycles of combined immunotherapy with ipilimumab and nivolumab and his successful treatment.

Case report

A 72-year-old Caucasian man, with a personal history of arterial hypertension and atrial fibrillation, first presented to the Oncology Department due to diagnosis of metastatic urothelial carcinoma. He had already undergone radical cystoprostatectomy and right uretero-nephrectomy revealing a pT3 high grade urothelial carcinoma of the bladder with clear surgical margins. In his CT staging metastatic lymphadenopathy was identified. His laboratory tests were within the normal ranges apart from serum creatinine, which was elevated (1.82 mg/dl, normal range 0.7–1.3 mg/dl).

Due to the findings of metastatic pelvic and retroperitoneal lymphadenopathy it was decided that systemic therapy would be the next step with the exception of cisplatin use due to his renal failure and former nephrec-

tomy. Ipilimumab 3 mg/kg and nivolumab 1 mg/kg combination for four cycles started on July 2018 and continued until the last dose was administered in late September 2018 with intervals of 21 days. His CT staging, after the completion of the four cycles of combined immunotherapy, revealed a significant response in all affected metastatic lymph nodes.

In early November 2018, in his scheduled follow-up visit, the patient complained about muscular weakness and maculopapular rash on his hands, thighs and face without any pruritus. His laboratory tests revealed elevated creatine kinase (CK) 1025 IU/L (normal range 24–195 IU/l). Skin biopsy was performed but was inconclusive. Methylprednisolone was administered due to suspected myositis related to immunotherapy administration. A dose of 48 mg per day was initiated with slow tapering of the dose and gradual improvement of the physical findings and a gradual decrease of CK. The patient continued with his scheduled follow-up visits where the CT scans always revealed stable disease, no findings of relapse and a gradually decreasing CK. In March 2019 the patient was urgently admitted to the Oncology Clinic due to fever, proximal muscle weakness and symptoms of dysphagia. The laboratory tests revealed again rising CK (725 IU/L) and elevated lactate hydrogenase (LDH) 294 IU/L (normal range 115–230 IU/l). This time his symptoms were more specific to possible dermatomyositis. Rheumatology consultation was conducted due to painless proximal muscle weakness along with the heliotropic rash around the eyes and periorbital edema that predominated on the upper eyelids. A raised erythematous scaly rash was also present on the extensor surface of the hands, compatible with Gottron's papules. A complete immunologic evaluation revealed positive antinuclear antibodies (ANA) at a titer of 1/320 and anti-transcriptional intermediary factor 1 γ (anti-TIF1γ) antibodies. Apart from clinical manifestations, muscle enzyme levels, and immunologic findings, the diagnosis of dermatomyositis was also established through muscle biopsy. Electromyography revealed sensorimotor neuropathy, partially attributed to prolonged corticosteroid administration. Due to the patient's renal failure, methotrexate was excluded as a possible therapeutic option and it was decided that intravenous immunoglobulin (IVIg) should be administered along with corticosteroids on a starting dose of 32 mg per day and with gradual tapering of the dose. The patient underwent five cycles of monthly IVIg at a dose of 400 mg/kg over a period of 5 consecutive days with significant clinical improvement and normalization of CK levels. In the meanwhile, all his CT scans performed for his urothelial carcinoma follow-up always reveal stable disease indicating no progression since the end of ipilimumab and nivolumab combination.

Discussion

Dermatomyositis and polymyositis are part of a rare, heterogeneous group of autoimmune myopathies [3]. Typical skin changes indicating dermatomyositis include a heliotrope rash of the upper eyelids and an erythematous rash which may be distributed over the joints. Gottron's papules refer to a characteristic rash found on the extensor surfaces of the small joints of the hands. This, along with the heliotrope rash of the eyelids, appears to be a disease-specific cutaneous finding [7]. Progressive, symmetric proximal muscle weakness is also a classic manifestation whereas dysphagia or dysarthria may also be present [8]. The main laboratory findings include elevated serum muscle-derived enzymes such as CK, LDH, aldolase as well as aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) while a pathognomonic muscle biopsy is also considered as one of the criteria for establishing the diagnosis [7, 9]. In the case of absence of cutaneous manifestations, the entity is called polymyositis. The underlying pathophysiology of the disease is not fully understood [10]. However, the presence of various autoantibodies, an association with specific, major histocompatibility genes, the demonstration of T-cell-mediated cytotoxicity of the muscle fibers, and the complement-mediated microangiopathy support an autoimmune etiology of this group of systemic diseases. Autoantibodies specific for autoimmune myopathies (myositis-specific autoantibodies) are clinically useful biomarkers to help to make the appropriate diagnosis; anti-Mi-2 is a classic marker for dermatomyositis [11].

An association between cancer and autoimmune myopathies, referred to as cancer-associated myositis, has been extensively reported in the medical literature; up to 20% of the cases with dermatomyositis may represent paraneoplastic manifestation of an underlying malignancy [12]. A pooled analysis by Hill *et al.* demonstrated that these systemic diseases strongly correlate with cancer. The onset of the disease can take place either before or after the diagnosis of the malignancy. The most common types of cancer associated with dermatomyositis were ovarian, lung, pancreatic, gastric and colorectal, whereas in the case of polymyositis non-Hodgkin lymphoma, lung, and bladder cancer were the predominant malignancies [13]. A more recent meta-analysis by Yang *et al.* demonstrated that both dermatomyositis and polymyositis are associated with increased risk of malignancy and specific-site cancers with the exception of gastric and prostate [14]. Male gender predominance was also demonstrated, despite the higher incidence of dermatomyositis and polymyositis in females. In both analyses, the number of bladder cancer cases was low. The strong correlation of these autoimmune, inflammatory myopathies with malignancies indicates their paraneoplastic background. The signs and symptoms of the autoimmune disease may have a parallel course with the malignancy and radical cancer therapy can lead to remission of the autoimmune mechanisms [14].

Anti-TIF-1γ is an antibody against a 155-kDa protein in patients with myositis that was first described in 2006 [15]. It has been hypothesized that it is involved in the transforming growth factor β pathway acting as either an agonist or antagonist of the pathway [16]. In a meta-analysis by Selva-O' Callaghan the presence of anti-TIF-1γ indicated an 18-fold increased association with malignancies [17]. The correlation of anti-TIF-1γ with malignancies in dermatomyositis/polymyositis patients has been further investigated and there are reports even supporting that

the presence of the antibody is so specific that its absence in patients with autoimmune disease can possibly rule out underlying cancer [18]. These data suggest that the presence of anti-TIF-1γ in cases of dermatomyositis/polymyositis strongly correlates with an underlying evident or occult malignancy and the autoimmune disease is probably a paraneoplastic manifestation [19].

Nivolumab, a human IgG4 monoclonal antibody, targets the PD-1 pathway and blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2, thus enhancing the immune response against cancer [20]. Ipilimumab, a human IgG1 monoclonal antibody against CTLA-4, also results in T-cell activation, leading to tumor cell rejection. Both immune checkpoint inhibitors enhance the host immune response against tumor cells [20]. Due to their immunomodulatory mechanism of action, several immune-related adverse events have been described [2]. Regarding ipilimumab, immune-related adverse events may occur in more than 65% of the patients, with the onset being placed within the first eight to twelve weeks after therapy initiation [2, 21]. In the case of nivolumab, the immune adverse events are less frequent compared to ipilimumab [2]. However, the combination of these two checkpoint inhibitors, first approved for metastatic melanoma, induced immune-related adverse reactions in 95% of the patients, with 55% of them being grade 3 or 4. In addition, the combination may cause immune-related adverse events over a prolonged time frame [2].

Among the different categories of adverse events attributed to immune checkpoint inhibitors, endocrinopathies, hepatitis, colitis, nephritis, and pneumonitis have been described as being more frequent [2]. Furthermore, rheumatologic adverse events including myalgias, arthralgias, myositis, vasculitis, polymyositis and temporal arteritis are also documented [22, 23]. However, dermatomyositis, when diagnosed in an oncologic patient, is usually attributed to the underlying malignancy and it is considered to be a paraneoplastic manifestation, due to the strong correlation of specific autoantibodies that were detected in our patient, as described above [12–14]. Nevertheless, it cannot be excluded as a type of possible immune-related adverse event in the context of immunotherapy administration.

In the last few years, there have been case reports of dermatomyositis/myositis in oncologic patients undergoing immunotherapy [24–28]. In a particular case, the identification of anti-TIF-1γ ultimately resulted in a final diagnosis of paraneoplastic dermatomyositis, although the onset of the disease was evident only after nivolumab administration [26]. In our case, the identification of anti-TIF-1γ in the patient's sera also contributed to the final diagnosis of a possible paraneoplastic dermatomyositis. Nonetheless, taking into consideration the immunomodulatory effects of the immune checkpoint inhibitors, the possibility of dermatomyositis being induced by the administration of ipilimumab and nivolumab cannot be ruled out. In the same aforementioned case by Shibata *et al.*, the patient's dermatomyositis symptoms onset was evident only after immunotherapy administration [26]. Taking into consideration that in our patient the same course of dermatomyositis took place, it is possible that checkpoint inhibitors induced dermatomyositis as an adverse event of immunotherapy.

Moreover, one must take into consideration the fact that a preexisting autoimmune disease might be exacerbated not only due to cancer itself, but also due to immunotherapy [29]. Our patient had a significant partial response of his disease after his therapy, which continues until today and with no evidence of disease flare. He did not undergo any other kind of immunotherapy or chemotherapy after the four cycles of ipilimumab and nivolumab administration. Dermatomyositis was manifested one month after the end of his therapy when his malignancy had reached is deepest response until today and, prior to the initiation of combined immunotherapy, there were no signs/symptoms or a history of a pre-existing systemic autoimmune disease. All this supports the hypothesis that dermatomyositis may be an adverse event driven by immunotherapy; implementing desirable antitumour responses by releasing the natural brakes of CTLA-4 and PD-1 signaling may lead to a substantial inflammatory burden. Given the current concepts regarding the multi-hit model of autoimmunity [30] and that autoimmune diseases often go through a preclinical stage in which specific autoantibodies are present but without overt clinical manifestations [31, 32], it can be hypothesized that our patient might have anti-TIF-1γ from the emergence of urothelial carcinoma. Activation of the complement presumably by these autoantibodies might have led to up-regulation of adhesion molecules on endothelial cells. The patient eventually developed features characteristic of dermatomyositis during the course of the disease, which might be due to T cell reactivity to muscle fibers, unleashed when combined PD-1 blocking and CTLA-4 blocking therapies were administered. The up-regulation of adhesion molecules on endothelial cells might have facilitated the migration of activated T cells to the perimysial and endomysial spaces, leading to full-blown autoimmunity and the development of dermatomyositis. Therefore, for oncologic patients undergoing immunotherapy a new landscape of adverse events is constantly evolving where more experience regarding the adverse events onset, diagnosis and therapy is of great need.

Conclusions

In the era of personalized medicine and immune checkpoint inhibitors, the spectrum of oncology therapy adverse events has changed. Immunomodulatory interventions in cancer patients provide significant benefit, but a new type of immune-related adverse events is in the spotlight. To our knowledge, this is the first case of dermatomyositis in a patient with bladder cancer after the completion of four cycles of combined immunotherapy with ipilimumab and nivolumab and his successful treatment. Autoimmune myopathies have been associated with underlying malignancies, either evident or occult, and more specifically dermatomyositis with anti-TIF-1γ is considered as a paraneoplastic manifestation. However, due to the ongoing expansion of use of immune checkpoint inhibitors

in many different neoplasms, clinicians must be aware of this entity. More research is needed on the pathogenetic significance of specific autoantibodies such as anti-TIF-1γ, associated with autoimmune myopathies and underlying malignancies, to be able to differentiate paraneoplastic manifestations from immune-related adverse events during checkpoint-blocking therapy, particularly in patients who might be at a preclinical stage of an autoimmune rheumatic disease.

The authors declare no conflict of interest.

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