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Case report

Rhabdomyolysis following single administration of pembrolizumab: Is severe immune-reaction a marker for durable treatment response?

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1. Background

Mismatch repair deficiency defines Lynch syndrome-associated malignancies and confers susceptibility to immune checkpoint inhibitors (ICIs), such as pembrolizumab. In endometrial cancers, long-term durable responses to immunotherapy have been documented (Chan et al., 2020). Toxicities related to ICIs are frequently of autoimmune etiology including rash, thyroid dysfunction, and gastrointestinal toxicity; however, more severe toxicities have been reported in multiple organ systems (Brooks et al., 2019). In a prior publication, Tomoaia et al. described a case of lethal myocarditis in a patient receiving immunotherapy with nivolumab and ipilimumab, demonstrating the potential for catastrophic adverse effects (Tomoaia et al., 2020).

We also present a rare case of ICI-related myopathy, albeit in a Lynch syndrome patient with synchronous gynecologic malignancies. This patient experienced a durable disease response after one dose, suggesting that severe toxicity might be an indicator of enduring immune modulation and extended disease control.

2. Case Report

Our patient is a 33-year-old, morbidly obese (BMI 55 mg/kg^2), nulliparous female with synchronous stage IA FIGO grade 2 endometrioid endometrial adenocarcinoma and stage IVB, HPV negative, moderately differentiated, squamous cell carcinoma of the vagina. Immunohistochemical analysis revealed loss of MSH 6 in both the vaginal and endometrial tumors with hormone receptor positivity in the endometrial mass only.

Imaging demonstrated metastatic disease to the bilateral external iliac lymph nodes, measuring 2.5 cm on the left and 2.6 cm on the right, as well as to a subcutaneous abdominal wall mass measuring 2.6 cm. On physical exam, an 8 cm exophytic mass was seen filling the vagina; biopsy of both the vaginal and abdominal wall masses showed squamous cell carcinoma. Pelvic lymph node biopsy was not performed as it would not have changed management, and it was felt that whichever primary had metastasized as far as the abdominal wall was likely to also be the one involving the pelvic nodes. Furthermore, the nodes were not easily accessible via a radiologic-guided procedure. In order to preserve fertility, a levonorgestrel-releasing intrauterine device was placed for treatment of her endometrial carcinoma, while systemic chemotherapy was started with intravenous (IV) cisplatin 50 mg/m^2, paclitaxel 135 mg/m^2, and bevacizumab 15 mg/kg given on a 21-day cycle. After three cycles, the vaginal mass had dwindled in size to 3 cm and was subsequently excised. Dilation and curettage was also performed. Neither specimen showed residual malignancy or dysplasia. Given her initial tolerance of chemotherapy and good response, 3 additional cycles of paclitaxel, bevacizumab, and cisplatin were planned. However, cisplatin was dropped for the 6th cycle due to cisplatin toxicity. Positron emission technology (PET) scan showed disappearance of the left inguinal lymph node and decrease of the right inguinal lymph node to 1.8 cm. The abdominal wall mass had similarly decreased in size to 1.2 cm upon completion of cytotoxic chemotherapy.

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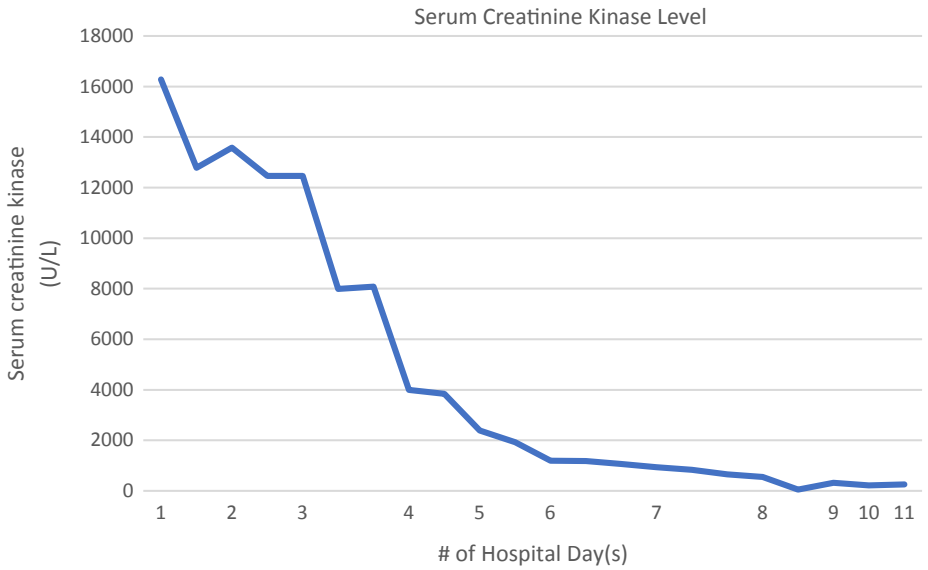

Fig. 1. Serum creatinine kinase trend (U/L) during admission while undergoing treatment; Peak value 16,280 U/L, Nadir value 51 U/L. Figure shows return to baseline in 9 days from beginning treatment.

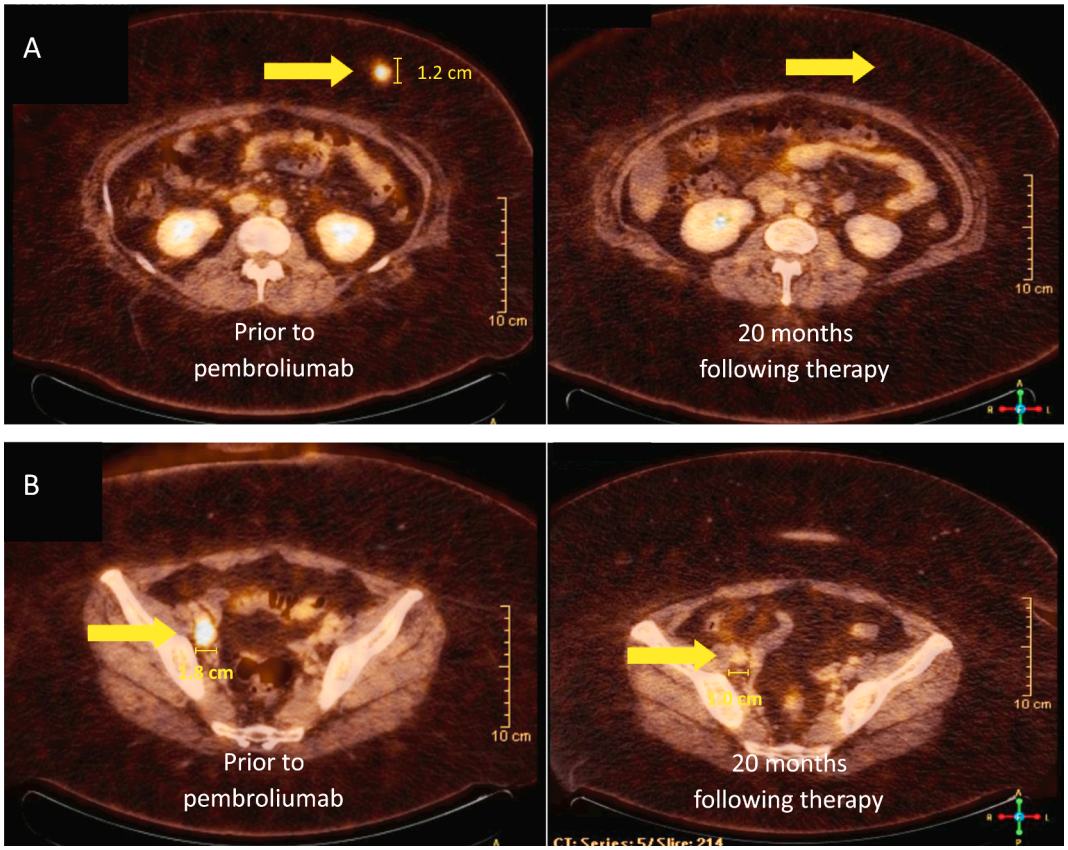

Fig. 2. (A) Pre-ICI PET-CT (left) shows metastasis to anterior abdominal wall 1.2 × 1.0 cm with SUV 6.4, with disappearance of this lesion on 20 month post-treatment scan (right); (B) Pre-ICI PET CT shows right external iliac lymph node with prominent hypermetabolism, 1.8 × 2.0 cm with SUV 12.5; 20 month post-treatment (right) shows decrease to 1.0 x 1.1cm with SUV 3.1.

We started IV pembrolizumab 200 mg after germline analysis confirmed a diagnosis of Lynch syndrome with a pathogenic mutation in MSH 6 (c2150_2153delTGAG). Eleven days after her first infusion, she presented with rapidly progressive proximal muscle weakness rendering her unable to walk. There were no other neurologic deficits including ptosis or diplopia. Blood work subsequently showed creatinine kinase (CK) of 16,280 U/L, strongly suggestive of rhabdomyolysis. Additionally, transaminases were elevated to 421 U/L (aspartate transaminase) and 156 U/L (alanine transaminase) with C-reactive protein elevated to 13.8 mg/L and erythrocyte sediment rate to 38 mm/hr. She was admitted for 11 days for aggressive fluid hydration with normal saline at 230 mL/hr and IV solumedrol 125 mg three times daily for 3 days. Fluids

and steroids were tapered as her CK decreased (Fig. 1). Rheumatology and neurology evaluated her for alternative etiologies including infection, hypothyroidism, myasthenia gravis, polymyositis, and Guillain-Barre Syndrome. TSH, electrolytes, and full auto-immune work-up were negative. Thus, she was presumptively diagnosed with common terminology criteria for adverse events grade 3 ICI-induced myositis. She received a 6-week prednisone taper on discharge, at which point CK had decreased to 271 U/L and she had returned to her prior functional status.

PET scan performed one month after hospital discharge demonstrated a partial response. Twenty months following a single pembrolizumab infusion, her exams, pap smears and endometrial biopsies remain normal. Her abdominal wall mass has resolved on the most recent PET (Fig. 2A) and the right pelvic lymph node which remains, now measuring 1 cm, has decreased both in size and metabolic activity (Fig. 2B). She is currently awaiting fertility planning with reproductive endocrinology.

3. Discussion

The above case is the first report describing severe immune-mediated myositis after a single dose of pembrolizumab. Katsuya et al. encountered severe myositis with CK elevated to >27,000 U/L only 10 days after the first infusion; however, this was attributed to nivolumab (Sakai et al., 2017). It is unclear if the same toxicity profiles apply to both nivolumab and pembrolizumab. Ours is also the first case to describe myositis in a patient with gynecologic cancer, as most reports focus on lung cancer or melanoma. It is especially surprising to see such a severe reaction in a young, healthy woman without prior medical conditions.

Interestingly, literature more frequently cites the co-occurrence of ICI-induced myopathies with other immune-mediated toxicity. Myositis is more often described accompanied by myasthenia gravis or cardiomyopathy, leading to respiratory failure (Shirai et al., 2016; Pourhassan et al., 2019). In these instances, myositis often portends poor outcomes (Shirai et al., 2016; Pourhassan et al., 2019). Myositis occurring in isolation, while more atypical, may be less grave.

There have been reports of full recovery, though these are the minority of cases (Min and Hodi, 2014). One case series detailed 6 patients, all with immune-mediated myositis after ICI therapy: 2 died, 3 made complete recoveries, and 1 was able to continue with ICI therapy (Shah et al., 2019). The 4 patients who improved had isolated myositis and did not show symptoms of cardiopulmonary disease.

Lastly, this case describes a potent and durable response to immunotherapy. Most authors describe death or progression of disease following ICI-induced myopathy. Min and colleagues are the only other group we found to describe durable response to immunotherapy following immune toxicity, however that was in the case of melanoma after 5 doses of nivolumab (Min and Hodi, 2014). No such responses have previously been seen in patients with gynecologic cancer or after a single dose of ICI. Liewluck et al. recounted one patient found to have no viable tumor on autopsy after pembrolizumab-induced myositis; however, that patient passed due to side effects, making tumor progression, in this case, clinically irrelevant (Liewluck et al., 2018).

In a review of 576 patients, Weber et all reported an association between immune-related side effects and improved response, noting greatest benefit in patients experiencing 3 or more immune-related toxicities, though with no impact on progression free survival (Weber et al., 2017). Our case supports the correlation between disease response and autoimmune side effects.

This report documents rhabdomyolysis as a rare adverse effect of pembrolizumab. This patient has stable disease, is no longer on any therapy, and is able to pursue fertility options. Such a robust response following one cycle of ICI adds to the evidence that severe toxicity, such as rhabdomyolysis, may be a corollary for excellent response to therapy and may represent sustained tumor-immunity. The repercussions of a reaction such as myositis may, in the long run, be a favorable trade-off if disease is significantly impacted.

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CRediT authorship contribution statement

Varun Khetan: Data curation, Writing - original draft. **Erin A. Blake:** Data curation. **Marcia A. Ciccone:** Conceptualization, Data curation, Formal analysis. **Koji Matsuo:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Brooks, R.A., Fleming, G.F., Lastra, R.R., Lee, N.K., Moroney, J.W., Son, C.H., et al., 2019. Current recommendations and recent progress in endometrial cancer. CA Cancer J. Clin. 69, 258–279.

Chan, J.K., Lakomy, D.S., McDonald, Y., Kapp, D.S., 2020. Long-term durable responses after pembrolizumab immunotherapy for recurrent, resistant endometrial cancer. Gynecologic Oncol. Reports 33, 100581.

Liewluck, T., Kao, J.C., Mauermann, M.L., 2018. PD-1 inhibitor-associated myopathies: emerging immune-mediated myopathies. J. Immunother. 41, 208–211.

Min, L., Hodi, F.S., 2014. Anti-PD1 following ipilimumab for mucosal melanoma: durable tumor response associated with severe hypothyroidism and rhabdomyolysis. Cancer Immunol. Res. 2, 15–18.

Pourhassan, H.Z., Tryon, D., Schaeffer, B., Mirshahidi, H., Wong, J., 2019. Autoimmune rhabdomyolysis and a multiorgan display of PD-1 inhibitor induced immune related adverse events during treatment of metastatic melanoma. Exp. Hematol. Oncol. 8, 20.

Sakai, K., Mochizuki, H., Mochida, K., Shiomi, K., Amano, M., Nakazato, M., 2017. A Case of Nivolumab-induced severe mononeuropathy multiplex and rhabdomyolysis. Case Rep. Med. 2017, 1093858.

Shah, M., Tayar, J.H., Abdel-Wahab, N., Suarez-Almazor, M.E., 2019. Myositis as an adverse event of immune checkpoint blockade for cancer therapy. Semin Arthritis Rheum. 48, 736–740.

Shirai, T., Sano, T., Kamijo, F., Saito, N., Miyake, T., Kodaira, M., et al., 2016. Acetylcholine receptor binding antibody-associated myasthenia gravis and rhabdomyolysis induced by nivolumab in a patient with melanoma. Jpn J. Clin. Oncol. 46, 86–88.

Tomoaia, R., Beyer, R.S., Pop, D., Minciuna, I.A., Dadarlat-Pop, A., 2020. Fatal association of fulminant myocarditis and rhabdomyolysis after immune checkpoint blockade. Eur. J. Cancer 132, 224–227.

Weber, J.S., Hodi, F.S., Wolchok, J.D., Topalian, S.L., Schadendorf, D., Larkin, J., et al., 2017. Safety profile of Nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J. Clin. Oncol. 35, 785–792.