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Title:

Immune Checkpoint Inhibitor-Induced Lymphocytic Fasciitis

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Abstract

We present the case of a 55-year-old man who presented with bilateral forearm pain two years after nivolumab treatment for melanoma. MRI and PET scan demonstrated

fasciitis, before confirmation of a florid lymphocytic infiltrate on biopsy. All symptoms resolved with immunosuppression. We discuss a unique complication of cancer immunotherapy.

A 55-year-old male with metastatic melanoma received nivolumab, an anti-programmed cell-death-protein-1 (anti-PD-1) immune checkpoint inhibitor (ICI), resulting in cancer remission. After two years he developed bilateral pain and tightness in his forearms and hands accompanied by paraesthaesia then diffuse arthralgia and myalgia. Examination revealed bilateral skin tightness and forearm induration with severe limitation of finger movement but no overt synovitis. Full blood examination showed a normal white cell count with marginally raised eosinophils, 0.6 x 10^9/L (0-0.5) and CRP, 30mg/L (<3); ANAs, ENAs, RF and ACPAs were not detected. Creatine kinase was normal. MRI revealed marked forearm fasciitis surrounding all muscle compartments, with no myositis (Figure 1). PET scan demonstrated remission of melanoma while confirming the fasciitis. Left forearm biopsy showed a florid lymphocytic fasciitis composed of predominantly T-cells and macrophages with scattered plasma cells and perivascular cuffing by lymphocytes in the deep subcutaneous tissue and underlying fascia (Figure 1). Eosinophils were not a feature and there was no fascial necrosis. Nivolumab was ceased and prednisolone 50mg daily commenced with methotrexate 20mg weekly. Symptoms resolved within two months apart from mild

restriction of hand movement. Prednisolone was tapered with no symptom recurrence. Repeat PET scan 10 months later showed no fasciitis or melanoma.

Immunotherapy has revolutionised the treatment of many cancers including melanoma. Prolonged survival is now a possibility due to ICIs[1]. Immune-related adverse events (IRAEs) are well-recognised complications, ranging from vitiligo to life-threatening colitis, hypophysitis and pneumonitis[2]. Arthralgia and myalgia occur in 20%[1] with other rheumatological IRAEs now increasingly recognised including de novo rheumatic diseases as well as flares of pre-existing conditions[3]. IRAEs identified include inflammatory arthritis, myositis, polymyalgia rheumatica, sicca syndrome and vasculitis.

We have presented a lymphocytic fasciitis secondary to ICI. Eosinophillic fasciitis after pembrolizumab (another ICI) was previously published[4]. That patient had widespread truncal and limb fasciitis, peripheral eosinophilia, 5.24 x 10^9/L (<0.5) and biopsy showing dense fascial infiltrate of eosinophils, plasma cells and lymphocytes. While neither high peripheral eosinophilia nor eosinophils on biopsy are essential to a diagnosis of eosinophilic fasciitis, the absence of both in our case combined with the histopathological findings and temporal relationship to nivolumab, leave an anti-PD-1-induced lymphocytic fasciitis as the

diagnosis. Interestingly the histology showed morphology atypical for eosinophillic fasciitis with florid lymphocytic infiltration as seen in other IRAEs in connective tissues (cardiac, skeletal muscle) following nivolumab[5,6].

Our patient responded to prednisolone and methotrexate. As with other ICI-induced rheumatic disease, early immunosuppression appears effective however several patients have required biologics[2,3]. Immunosuppression must be balanced against the risk of cancer progression or recurrence. Reintroduction of nivolumab was not required in this case as remission was sustained. While many of the IRAEs occur early after ICI use, rheumatological manifestations may appear late or after cessation[3].

The phenomenal success of immunotherapies in oncology means their use is rising dramatically. IRAEs are therefore expected to increase in prevalence including rheumatological manifestations. Clinicians should be aware of IRAEs to optimise patient outcome with early treatment institution.

References

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Figure Legends

Figure 1: (A, B) T2 MRI showing extensive inflammation (marked hyperintensity and enhancement) involving the fascia surrounding all of the forearm muscle compartments. Inflammation also affects the flexor and extensor tendon sheaths in the distal forearm, but the muscles are spared. (C) Forearm biopsy haematoxylin and eosin stained section showing fascia with a prominent infiltrate of lymphocytes. (D) CD3 immunoperoxidase study showing the dominant lymphocyte is a T-lymphocyte.

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We present the case of a 55-year-old man who presented with bilateral forearm pain two years after nivolumab treatment for melanoma. MRI and PET scan demonstrated fasciitis, before confirmation of a florid lymphocytic infiltrate on biopsy. All symptoms resolved with immunosuppression. We discuss a unique complication of cancer immunotherapy.

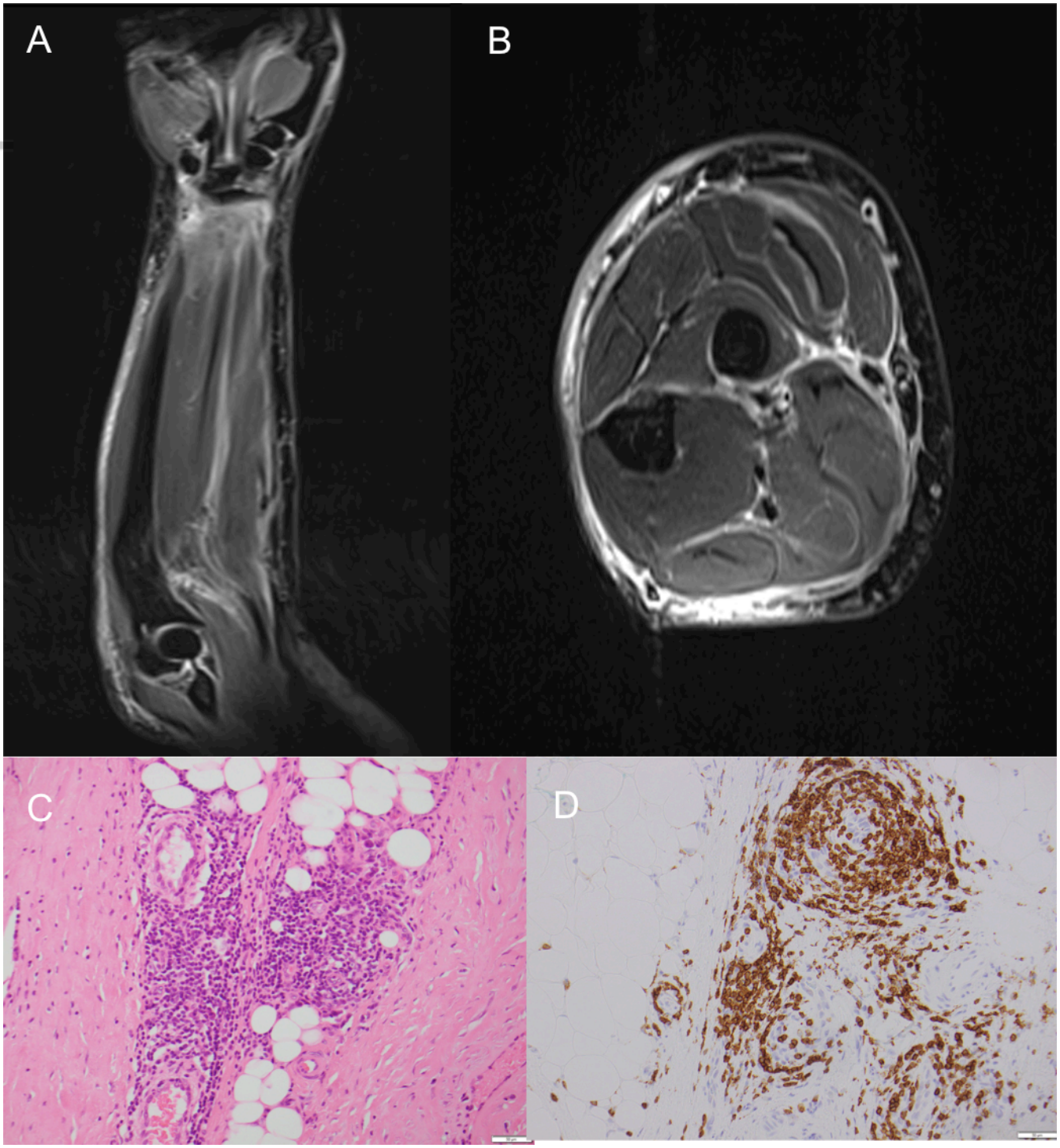

Figure 1.tiff

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