

New onset polyarthritits secondary to pembrolizumab [anti-PD1 antibody] in a patient with metastatic melanoma successfully treated with IL-6 receptor [IL-6R] inhibitor.

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Introduction

- Programmed cell death 1 (PD-1) a transmembrane protein expressed on T cells, B cells, and NK cells is an inhibitory molecule that binds to PD-ligand 1 and 2.
- PD-L1 is expressed on the surface of multiple tissue types, including many tumor cells.
- The PD-1-PD-L1/2 interaction directly inhibits apoptosis of the tumor cells.
- Targeted therapies such as pembrolizumab an anti PD-1 antibody interfere with crucial molecular events in tumor cells that control tumor growth and invasion.
- Since its FDA approval in 2014, pembrolizumab, has proven to be an effective treatment option for patients with metastatic melanoma.

- Indications for PD-1/L1 blocking agents are rapidly growing; Its recent approval for non-small cell carcinoma is changing the way this cancer is now treated. In the near future indications for lymphoma, kidney, bladder and other cancers are soon to follow.
- Patients treated with anti-PD-1/L1 therapy are prone to develop autoimmune toxicities like: skin rash, colitis, pneumonitis hepatitis, nephritis, endocrinopathies, musculoskeletal manifestations such as arthritis, lupus like and myopathies.

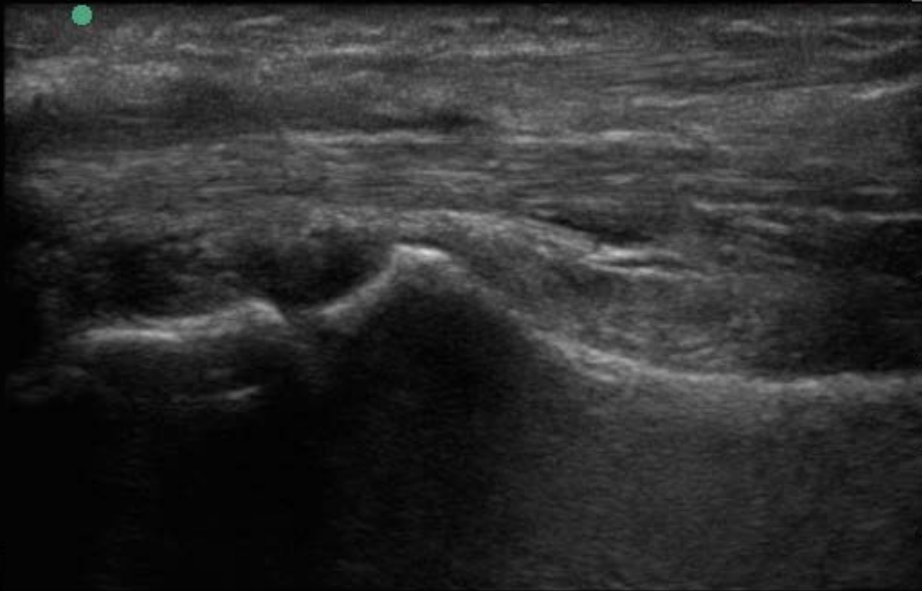
- Cancer incidence continues to increase worldwide; therefore a substantial number of patients will be exposed to these blocking monoclonal antibodies hence adverse events will also increase.
- Here we present a case of musculoskeletal toxicities.

Patient presentation

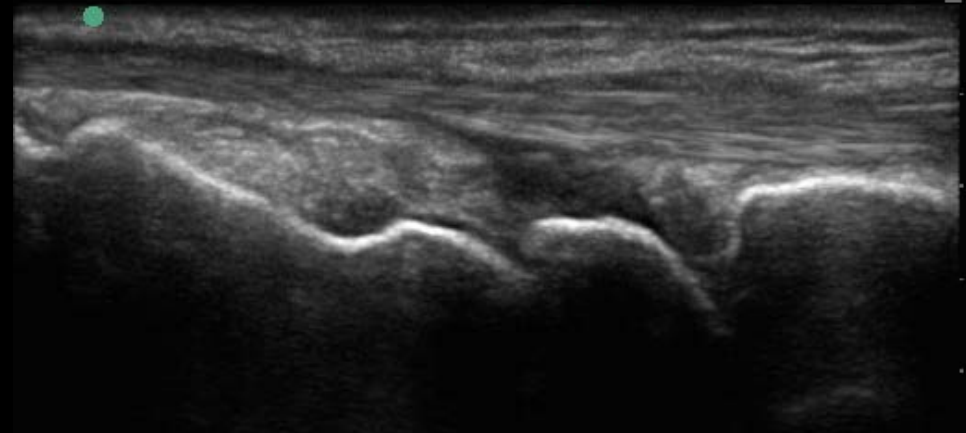
- Patient is 63 y/o white male with a diagnosis of metastatic melanoma who progressed on prior chemotherapy and ipilimumab and currently treated with pembrolizumab.
- He presented to the rheumatology clinic with fatigue, myalgia and debilitating symmetric poly-arthritis of the MCPs, PIPs, wrists, ankles and knees after his second dose of pembrolizumab.
- Given the severity of his symptoms he was wheel chair bound and his anti PD-1 treatment was withheld. He was subsequently treated with other chemotherapeutic agents but experienced further progression of melanoma.
- His arthritis was initially treated with high dose prednisone resulting in partial resolution of his symptoms. However the patient was unable to taper prednisone less than 20 mg/day without severe exacerbation of symptoms.

- Physical exam revealed synovitis of the wrists, MCPS, PIPs, knees and ankles.

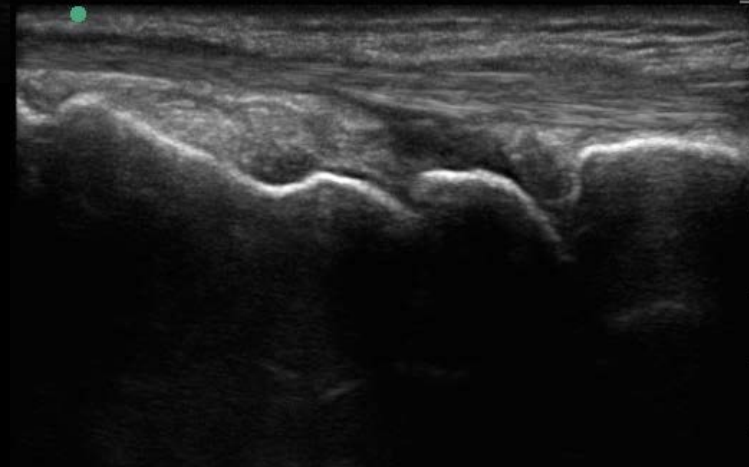
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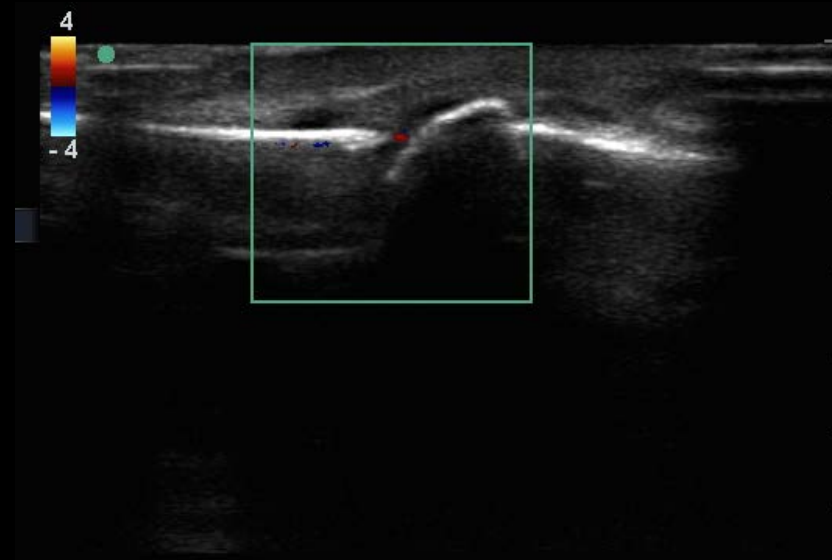
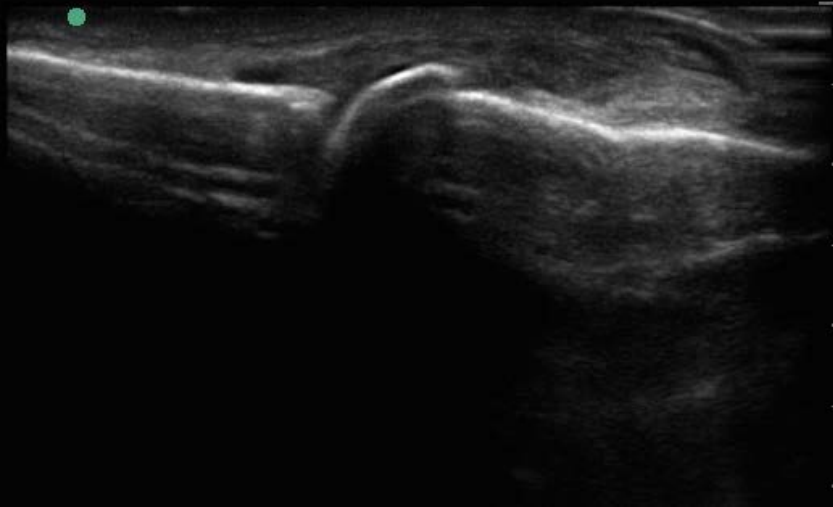
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DORSAL LONG RIGHT WRIST|



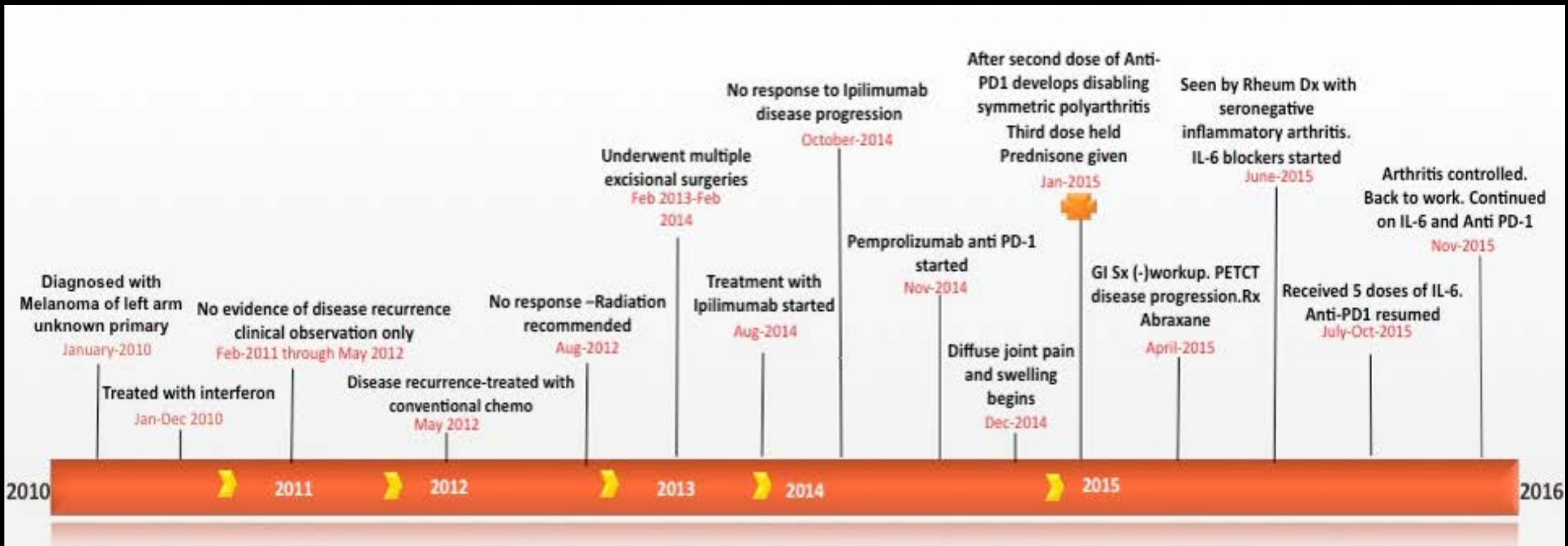
RIGHT SECOND MCP



- Laboratory work up demonstrated negative ANA, RF and anti-CCP, X ray images revealed no significant abnormalities.
- Our working diagnosis, given the negative work up, was anti PD-1 induced polyarthritis.
- Decided to treat with tocilizumab 162 mg subQ weekly along with low dose prednisone 10mg /day.

- After four doses of tocilizumab his symptoms improved significantly to the point that he was fully functional and returned to work.
- Pembrolizumab was resumed and his melanoma is now better controlled.
- Around his tenth dose of tocilizumab he developed severe abdominal pain with negative findings, however was found to have mild thrombocytopenia and his treatment was changed to every other week with same dosage.
- He is currently tolerating both agents well and is fully functional.

Timeframe



Discussion

- Anti-PD-1/L1 cancer therapy predisposes patients to develop immune-related adverse events (irAEs) like: skin rash, colitis, pneumonitis, hepatitis, nephritis, hypophysitis, hypothyroidism, musculoskeletal manifestations such as arthritis, lupus like autoimmune disease and myopathies.
- Mild to moderate toxicities are usually managed with supportive care alone, withholding immunotherapy, and or a short course of low dose corticosteroids.
- Its believed that short course low dose steroids still allows the possibility of a tumor response to treatment.

Semin Oncol. 2015;42(3):423-8, Semin Oncol.
2015;42(4):587-600. N Engl J Med. 2012;366(26):2443-
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Ann Oncol. 2015;26(12):2375.

- For severe or life threatening irAEs like: pneumonitis and severe colitis, the cancer immunotherapy is withheld and high dose steroids along with aggressive immunosuppression is given.
- Frequently used for such irAEs: Infliximab and mycophenolate mofetil have shown to be effective treatments.
- There are concerns with the use of such broad immunosuppression would interfere with cancer immunotherapy tumor response.

Decision to treat with Tocilizumab

- Our patient had significant irAEs but were not life threatening to warrant aggressive broad immunosuppression like infliximab.
- Initially treated with moderate to high dose steroids with potential interference with cancer therapy and without fully controlling his symptoms.
- By inhibiting IL-6 we targeted a specific pathway that is known to be involved in many inflammatory conditions, at the same time sparing other pathways needed for tumor response.

Conclusions

- In this case of anti PD-1 induced polyarthritits, IL-6R inhibitor, tocilizumab has proven to be an effective treatment without compromising the efficacy of this cancer therapy.
- To our knowledge this is the first case of anti PD-1 induced arthritis treated successfully with IL-6R inhibitors.
- Patients on anti PD-1 therapies should be monitored closely for the development of autoimmune toxicities.
- Further investigations and controlled prospective clinical trials are needed to further validate this approach.

References

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