American Journal of Ophthalmology Case Reports 36 (2024) 102025

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Periocular granulomatous inflammatory lesions mimicking conjunctival melanoma recurrence in the setting of systemic nivolumab treatment

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ARTICLE INFO

Keywords:
Conjunctival melanoma
Immune checkpoint inhibitors
Nivolumab
Granulomatous inflammation
Sarcoid-like granuloma
Immune-related adverse effect

ABSTRACT

Purpose: Conjunctival melanoma is a rare neoplasm with high rates of recurrence and metastasis. Traditional management includes surgical excision and cryotherapy, followed by adjuvant therapy as needed. Immune checkpoint inhibitors, including nivolumab, are a targeted treatment option with improved survival rates. However, various immune-related adverse effects have been reported with these drugs. While systemic granulomatous inflammation is a documented systemic side effect, it has rarely been reported in the conjunctiva and ocular adnexa.

Observation: A patient with a history of recurrent metastatic conjunctival melanoma presented with both a left sub-conjunctival and upper eyelid lesion after the commencement of treatment with nivolumab. The lesions were excised with a clinical suspicion for metastasis and consisted of noncaseating granulomatous inflammation with no evidence of malignancy on histopathologic examination. Infectious and primary autoimmune etiologies were ruled out.

Conclusion and importance: This is a biopsy-proven case of periocular immune checkpoint inhibitor-associated granulomatous inflammation.

1. Introduction

Conjunctival melanoma is a rare and potentially deadly tumor with an incidence of 0.4 per million and a mortality rate of 30%.[1] Clinically, the tumors are staged according to their location and size. Histologically, the tumor thickness, morphology (epithelioid presence/absence), mitotic count, and margin status are variables accounted for in prognostication.[2] Treatment of conjunctival melanoma includes wide surgical excision accompanied by cryotherapy. The recurrence rate ranges from 36 to 62%, while metastasis develops in 20–30% of patients.[1] Because these lesions have a high rate of recurrence and metastasis, adjuvant therapy with topical chemotherapy, focal cryotherapy, and radiotherapy are often utilized, and orbital exenteration may be required. Recent developments in immunotherapy have expanded treatment options to include immune checkpoint inhibitors (ICIs).[3–5] These drugs have been very effective in reducing the morbidity and mortality of this aggressive disease. Herein, the authors describe a patient with a history of malignant conjunctival melanoma who presented with new lesions of the inferior fornix and the left upper eyelid after undergoing nivolumab treatment. Initially thought to be new metastatic lesions, the excisional biopsies confirmed granulomatous, sarcoid-like inflammation and no malignancy. The clinical, radiographic, histologic, and immunohistochemical investigation conducted to differentiate these lesions from recurrent melanoma is discussed. This report adheres to the Declaration of Helsinki and complies with the Health Insurance Portability and Accountability Act.

2. Case report

A 46-year-old male with a history of malignant conjunctiva melanoma of the left eye presented with a pigmented conjunctival lesion in the inferior fornix and an enlarging left upper eyelid lesion. He was status post excision of a conjunctival melanoma with positive margins and subsequent metastasis to the submandibular lymph node, left upper

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https://doi.org/10.1016/j.ajoc.2024.102025
Received 22 December 2023; Accepted 9 February 2024
Available online 18 February 2024

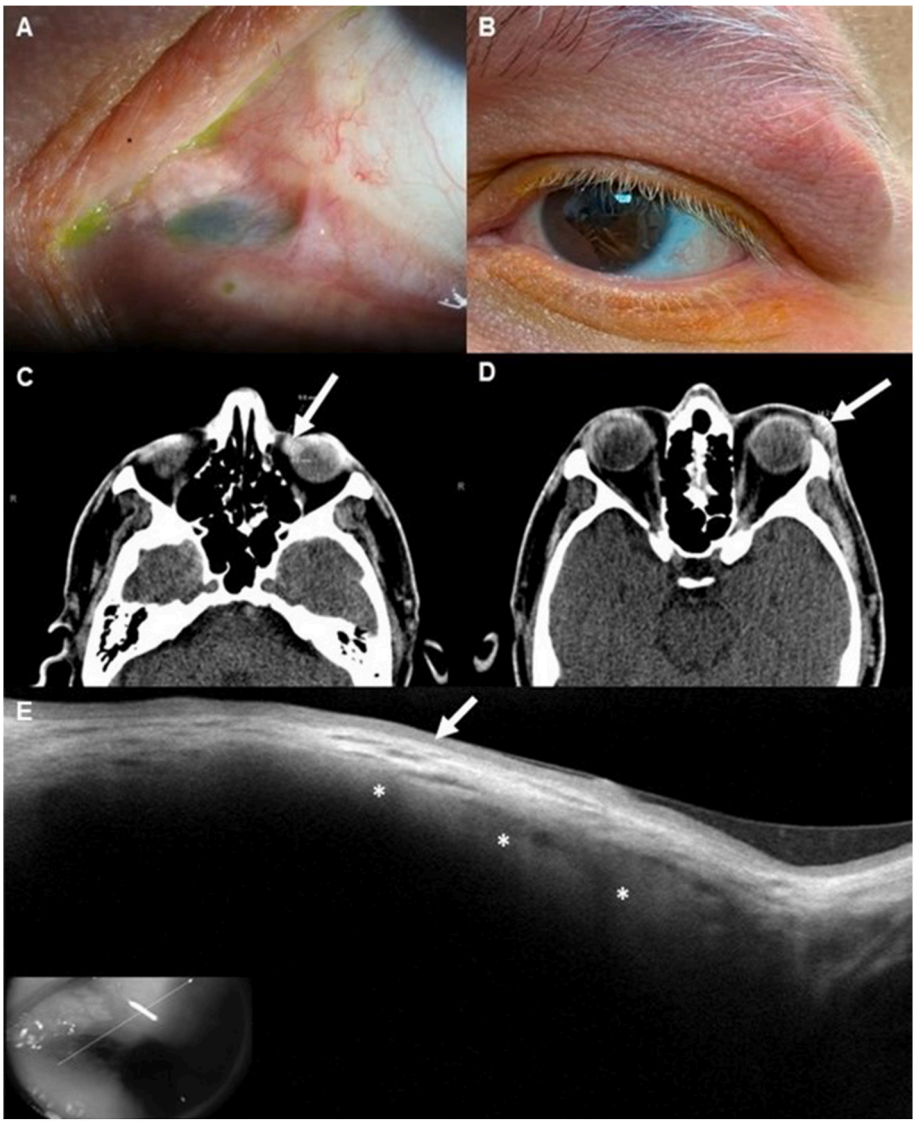

Fig. 1. A) The slit lamp photograph demonstrates a subepithelial brown-green lesion in the inferonasal fornix with adjacent symblepharon present on the temporal aspect of the lesion. B) The slit lamp photograph demonstrates a variably firm subcutaneous supertemporal left upper eyelid lesion. C) CT scan demonstrates left anterior-inferior medial orbital soft tissue mass measuring 1.0 cm in diameter (arrow). D) CT scan demonstrates left lateral periorbital soft tissue mass measuring 1.4 cm in diameter (arrow). E) Anterior segment OCT demonstrates normal thickness epithelium (arrow) and a subepithelial hyper-reflective lesion with posterior shadowing (asterisks).

eyelid, and lung. On examination, his visual acuity was 20/20 in both eyes. Pupils were equal, round, and reactive to light. Intraocular pressures were 16 mmHg bilaterally. Slit lamp examination demonstrated inferior forniceal scarring and shortening nasally. An inferonasal brown-green, flat sub-epithelial lesion was present in the fornix (Fig. 1A). A variably firm left upper eyelid lesion was present laterally (Fig. 1B). The external examination was significant for an enlarged left cervical lymph node. Computed tomography (CT) of the orbit demonstrated a left anterior-inferior medial orbital soft tissue mass measuring 1.0 cm (Fig. 1C). A 1.4 cm hyperdense left lateral periorbital soft tissue mass was also noted (Fig. 1D). Anterior segment optical coherence tomography (AS-OCT) demonstrated unremarkable epithelium with an underlying hyper-reflective subepithelial lesion with significant posterior shadowing (Fig. 1E).

The patient was initially diagnosed with conjunctival melanoma four years prior to presentation of these eyelid and forniceal lesions. At the initial presentation of the melanoma, he underwent excision in his native country with pathology demonstrating malignant BRAF positive melanoma at least 2.3 mm in thickness with extension to multiple margins. Upon referral to our center, map biopsies were performed to identify sites of residual melanoma, and one out of the 13 specimens demonstrated atypical intraepithelial melanocytic proliferation. This area of suspected residual melanoma was then completely excised. Later that year, he developed a metastatic melanoma lesion in a submandibular lymph node, which was excised and found to be BRAF positive. Despite treatment with cryotherapy, mitomycin-C, and systemic dabrafenib and trametinib, three years later he developed a new rubbery mass of the supratemporal orbit, causing ptosis. This orbital mass was excised, and pathologic examination demonstrated malignant melanoma consistent with metastasis with extension to at least one margin. The following month, a chest CT demonstrated multiple pulmonary nodules measuring up to 10 mm, scattered bilaterally, suggestive of metastasis. A wedge resection of the patient's left lower lobe was performed and demonstrated metastatic malignant melanoma. He was then enrolled in a research protocol and underwent three cycles of UV1 vaccination with nivolumab 1 mg/kg and ipilimumab 3 mg/kg. He continued nivolumab 480 mg for maintenance therapy.

Five months after commencing treatment with nivolumab, the

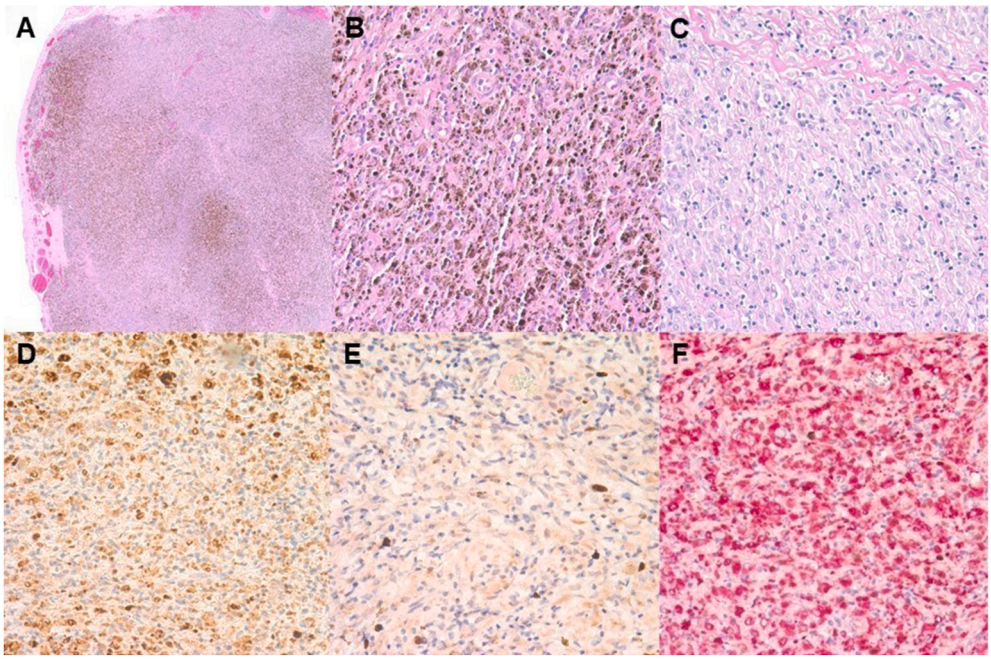

Fig. 2. Left inferior medial fornix lesion: A) Low power histopathologic examination discloses fibrovascular tissue with a subepithelial infiltrate of basophilic and eosinophilic cells and variable amount of pigment deposition (H&E, original magnification ×40). B) Higher power examination demonstrates intra- and extracellular brown pigment granules consistent with melanin (H&E, original magnification ×400). C) Bleach-prepared morphological evaluation demonstrates the cells to consist of bland round nuclei with lack of prominent nucleoli, pleomorphism, and mitotic activity (Bleach, original magnification ×400). D) SOX-10 and E) Melan-A are negative, confirming no evidence of melanoma (SOX-10, original magnification ×400; Melan-A with red chromogen, original magnification ×400). F) CD68 stain highlights granulomatous inflammation composed of a diffuse infiltrate of histiocytes (CD68 with red chromogen, original magnification ×400).

patient again presented with new inferior forniceal and upper eyelid lesions. Given the patient's extensive history of metastatic malignant melanoma, the presumption was further metastatic disease. He underwent excisional biopsies of both periocular lesions for diagnostic purposes. Histopathologic examination of the conjunctival lesion demonstrated a marked amount of brown pigment concerning the recurrence of conjunctival melanoma (Fig. 2A and B). However, upon review of bleach-stained slides, the sample consisted of morphologically benign appearing cells (Fig. 2C). Immunohistochemical staining with SOX-10 and Melan-A markers was negative, which ruled out a melanocytic lesion (Fig. 2D and E). CD68 immunohistochemical staining demonstrated the bland cells to be histiocytic in origin (Fig. 2F). The upper eyelid lesion demonstrated a similar staining pattern (Fig. 3A–C). The conjunctival and upper eyelid lesions were found to be noncaseating granulomatous inflammation.

The presence of granulomatous inflammation raised suspicion for infectious, autoimmune, and neoplastic processes. Ziel-Nielson and Grocott methenamine silver stains were performed to rule out fungal and mycobacterial infections. Other neoplastic processes were also ruled out due to the lack of morphologic or immunohistochemical evidence for malignancy. Furthermore, systemic evaluations for sarcoidosis, lupus, and rheumatoid arthritis were negative, decreasing the likelihood of a primary autoimmune etiology. Birefringent foreign material was present in the eyelid lesion; however, a foreign body reaction does not explain the degree of inflammation (Fig. 3D). Additionally, foreign material was not present in the conjunctival lesion. After ruling out all other causes, the etiology of the granulomatous inflammation was suspected to be medication-induced due to ICI therapy. Once it was confirmed that the new lesions were not metastasis, the patient continued nivolumab treatment with resolution of his lung nodules and no other inflammatory reactions.

3. Discussion

The efficacy of ICIs has been described in the treatment of conjunctival melanomas in several case series.[6–8] Nivolumab, a programmed cell death-1 (PD-1) inhibitor that reverses the suppression of T cells to potentiate anti-tumor immune responses is commonly used with favorable outcomes of halting disease progression and increasing survival rates.[9] While demonstrating promising results, side effects resembling autoimmune disease have been reported with ICI use and occur in up to 64% of nivolumab-treated cutaneous melanoma cases.[5] Nivolumab has been shown to cause sarcoid-like granulomas (SLG) affecting the skin, lymph nodes, and lung.[10–13] These SLGs are masses that may initially be confused with a recurrent or metastasis, although biopsy demonstrates a lesion consisting of granulomatous inflammation with no evidence of malignancy.

Ocular immune-related adverse events (IRAEs) are less frequently observed and occur in approximately 1% of patients treated with ICIs.[5] Uveitis is the most reported side effect of PD-1 inhibitors, with anterior, Vogt-Koyanagi-Harada-like, and panuveitis occurring more often.[14] Neuro-ophthalmic, corneal and ocular surface, orbital and ocular adnexal, and retinal complications have also been described, with myasthenia gravis, dry eye, acute macular neuroretinopathy, and myositis being the most common manifestations, respectively.[14–19] While the pathogenesis of ophthalmic IRAEs is not well elucidated, it is thought to result from T cell response to both tumor and normal cells. In systemic sarcoidosis, a hyperactive pro-inflammatory T helper-1 (Th-1) and T helper-17 (Th-17) immune response can lead to granulomatous inflammation and cause similar symptoms as the widely reported IRAEs of PD-1 inhibitors. Thus, Rambhia et al. proposed that the sarcoid-like granulomatous inflammation in PD-1 inhibitor-treated patients occurs in the setting of heightened Th-1/Th-17 immune response, similar to the cytokines distributed in sarcoidosis.[20]

4. Conclusions

After conducting a literature review in December 2023 utilizing PubMed using the keywords "granulomatous inflammation," "immune checkpoint inhibitor," and "eye/ocular," we did not find any prior

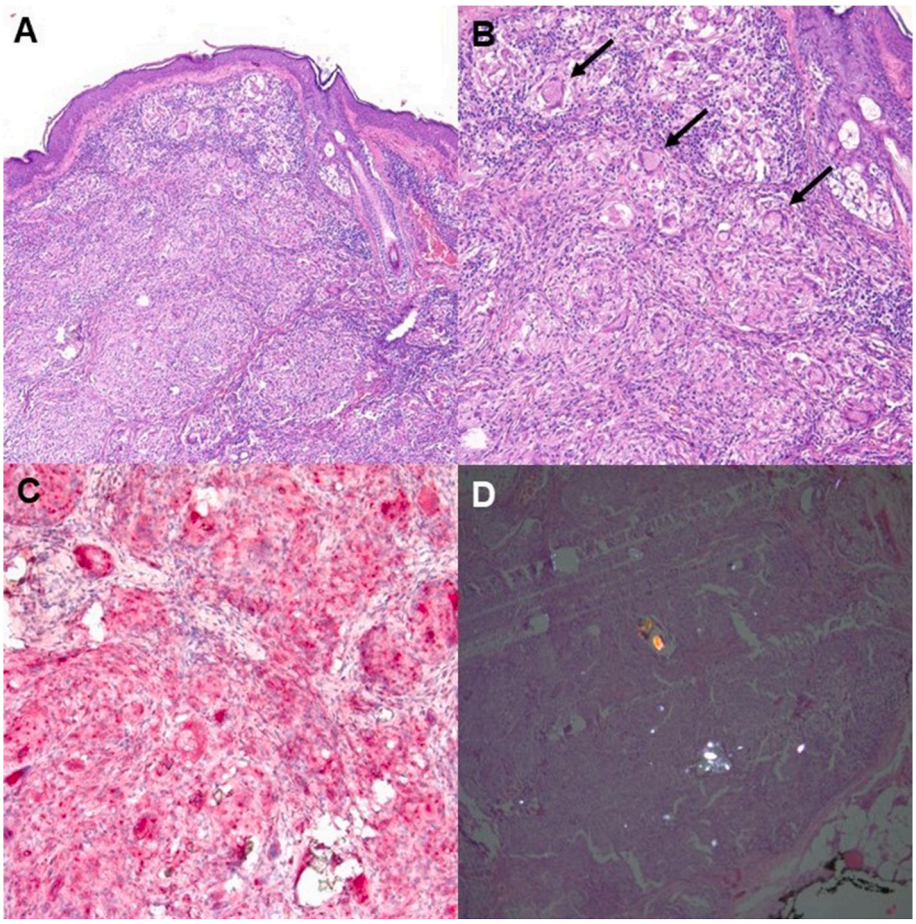

Fig. 3. Left upper eyelid lesion: A) Low power histopathologic examination discloses an intradermal infiltrate of noncaseating granulomatous inflammation composed of epithelioid histiocytes, foreign body, and Langhans giant cells with surrounding areas of morphologically benign lymphocytes (H&E, original magnification ×100). B) Higher power examination demonstrates a histiocytic infiltrate with foci of giant cells (arrows, H&E, original magnification ×200). C) The diffuse histiocytic infiltrate with foci of giant cells is highlighted by CD68 stain (CD68 with red chromogen, original magnification ×200). D) Multiple foci of birefringent foreign material are visualized with polarized light (H&E with polarized light, original magnification ×100).

reports of biopsy-proven cases of noninfectious granulomatous inflammation associated with ICI in the ocular adnexa. Given the history of nivolumab treatment, the pathological findings are consistent with sarcoid-like granulomatous inflammation described in ICI-treated patients. The morphologically benign histiocytes and pigment-containing cells representing tumoral melanosis present in the conjunctival lesion are likely a result of the involution of the conjunctival melanoma associated with ICI usage. To guide treatment, physicians should know the potential inflammatory or autoimmune sequelae induced by immunomodulatory therapies. New masses in a patient on an ICI for metastatic melanoma may require biopsy to determine if the lesion represents an inflammatory IRAE or a recurrent melanoma and treatment failure.

Patient consent

The patient consented to the publication of the case orally.

CRediT authorship contribution statement

Charissa H. Tan: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Yoseph Sayegh:** Data curation, Formal analysis, Investigation. **Sohaib Fasih-Ahmad:** Data curation, Investigation. **David T. Tse:** Data curation, Validation. **Carol L. Karp:** Conceptualization, Formal analysis, Methodology. **Sander R. Dubovy:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft.

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.

Acknowledgements and Disclosures

Funding: NIH Center Core Grant P30EY014801, The RPB Unrestricted Award and Career Development Awards, Dr. Ronald and Alicia Lepke Grant, The Lee and Claire Hager Grant, The Grant and Diana Stanton-Thornbrough, The Robert Baer Family Grant, The Emilyn Page and Mark Feldberg Grant, The Robert Farr Family Grant, The Jose Ferreira de Melo Grant, Mr. and Mrs. Irwin Friedman Grant, The Roberto and Antonia Menendez Family Grant, The Stephen Takach Grant, The Richard and Kathy Lesser Grant, The Ragheb Family Grant, The Honorable A. Jay Cristol Grant, The Michele and Ted Kaplan Grant, The Christian Kathke Grant, The Carol Soffer Grant, and the Richard Azar Family Grant (institutional grants).

List of abbreviations

ICI	Immune checkpoint inhibitors
AS-OCT	Anterior segment optical coherence tomography

CT	Computed tomography
PD-1	Programmed cell death-1
SLG	Sarcoid-like granulomas
IRAE	Immune-related adverse events
Th-1	T helper-1
Th-17	T helper-17

References

1. Kaštelan S, Gverović Antunica A, Beketić Orešković L, Salopek Rabatić J, Kasun B, Bakija I. Conjunctival melanoma - epidemiological trends and features. *Pathol Oncol Res*. 2018/10//2018;24(4):787–796. https://doi.org/10.1007/S12253-018-0419-3.
2. Jain P, Finger PT, Damato B, et al. Multicenter, international assessment of the eighth edition of the American joint committee on cancer cancer staging manual for conjunctival melanoma. *JAMA Ophthalmol*. 2019/8//2019;137(8):905–911. https://doi.org/10.1001/JAMAOPHTHALMOL.2019.1640.
3. Gkiala A, Palioura S. Conjunctival melanoma: update on genetics, epigenetics and targeted molecular and immune-based therapies. *Clin Ophthalmol*. 2020;14:3137–3152. https://doi.org/10.2147/OPTH.S271569.
4. Grimes JM, Shah NV, Samie FH, Carvajal RD, Marr BP. Conjunctival melanoma: current treatments and future options. *Am J Clin Dermatol*. 2020/6//2020;21(3):371–381. https://doi.org/10.1007/S40257-019-00500-3.
5. Brouwer NJ, Verdijk RM, Heegaard S, Marinkovic M, Esmaeli B, Jager MJ. Conjunctival melanoma: new insights in tumour genetics and immunology, leading to new therapeutic options. *Prog Retin Eye Res*. 2022. https://doi.org/10.1016/J.PRETEYERES.2021.100971, 1//2022;86.
6. Ford J, Thuro BA, Thakar S, Hwu WJ, Richani K, Esmaeli B. Immune checkpoint inhibitors for treatment of metastatic melanoma of the orbit and ocular adnexa. *Ophthalmic Plast Reconstr Surg*. 2017;33(4):e82–e85. https://doi.org/10.1097/IOP.0000000000000790.
7. Finger PT, Pavlick AC. Checkpoint inhibition immunotherapy for advanced local and systemic conjunctival melanoma: a clinical case series. *J Immunother Cancer*. 2019/3//2019;7(1). https://doi.org/10.1186/S40425-019-0555-7.
8. Sagiv O, Thakar SD, Kandl TJ, et al. Immunotherapy with programmed cell death 1 inhibitors for 5 patients with conjunctival melanoma. *JAMA Ophthalmol*. 2018/11//2018;136(11):1236–1241. https://doi.org/10.1001/JAMAOPHTHALMOL.2018.3488.
9. Sa HS, Daniel C, Esmaeli B. Update on immune checkpoint inhibitors for conjunctival melanoma. *J Ophthalmic Vis Res*. 2022/7//2022;17(3):405–412. https://doi.org/10.18502/JOVR.V17I3.11579.
10. Danlos FX, Pagès C, Baroudjian B, et al. Nivolumab-induced sarcoid-like granulomatous reaction in a patient with advanced melanoma. *Chest*. 2016/5//2016;149(5):e133–e136. https://doi.org/10.1016/J.CHEST.2015.10.082.
11. Noguchi S, Kawachi H, Yoshida H, et al. Sarcoid-like granulomatosis induced by nivolumab treatment in a lung cancer patient. *Case Rep Oncol*. 2018/5//2018;11(2):562–566. https://doi.org/10.1159/000492383.
12. Ogawa T, Ishitsuka Y, Iwamoto K, et al. Programmed cell death 1 blockade-induced cutaneous sarcoid-like epithelioid granulomas in advanced melanoma: a case report. *J Eur Acad Dermatol Venereol : JEADV*. 2018/7//2018;32(7):e260–e261. https://doi.org/10.1111/JDV.14781.
13. Mobini N, Dhillon R, Dickey J, Spoon J, Sadrolashrafi K. Exclusive cutaneous and subcutaneous sarcoidal granulomatous inflammation due to immune checkpoint inhibitors: report of two cases with unusual manifestations and review of the literature. *Case Rep Dermatolo Med*. 2019;2019. https://doi.org/10.1155/2019/6702870.
14. Martens A, Schauwvlieghe PP, Madoe A, Casteels I, Aspeslagh S. Ocular adverse events associated with immune checkpoint inhibitors, a scoping review. *J Ophthalmic Inflammat Infect*. 2023/12//2023;13(1). https://doi.org/10.1186/S12348-022-00321-2.
15. Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA. Checkpoint inhibitor immune therapy: systemic indications and ophthalmic side effects. *Retina*. 2018;38(6):1063–1078. https://doi.org/10.1097/IAE.0000000000002181, 2018/6//.
16. Kim JM, Materin MA, Sznol M, et al. Ophthalmic immune-related adverse events of immunotherapy: a single-site case series. *Ophthalmology*. 2019/7//2019;126(7):1058–1062. https://doi.org/10.1016/J.OPHTHA.2019.01.031.
17. Fang T, Maberley DA, Etminan M. Ocular adverse events with immune checkpoint inhibitors. *J Current Ophthalmol*. 2019/9//2019;31(3):319–322. https://doi.org/10.1016/J.JOCO.2019.05.002.
18. Philip AM, Anesi SD, Foster CS, Chang P. Ocular inflammatory complications of treatment for metastatic melanoma. *Ocul Immunol Inflamm*. 2022. https://doi.org/10.1080/09273948.2022.2098147.
19. Mazharuddin AA, Whyte AT, Gombos DS, et al. Highlights on ocular toxicity of immune checkpoint inhibitors at a US tertiary cancer center. *J Immunotherapy Precision Oncol*. 2022/11//2022;5(4):98–104. https://doi.org/10.36401/JIPO-22-14.
20. Rambhia PH, Reichert B, Scott JF, et al. Immune checkpoint inhibitor-induced sarcoidosis-like granulomas. *Int J Clin Oncol*. 2019/10//2019;24(10):1171–1181. https://doi.org/10.1007/S10147-019-01490-2.