Current Rheumatology Reports (2019) 21: 28
https://doi.org/10.1007/s11926-019-0828-7

VASCULITIS (L ESPINOZA, SECTION EDITOR)

Systemic Vasculitis Associated With Immune Check Point Inhibition: Analysis and Review

Teresa M Crout[1] · Day S Lennep[1] · Shweta Kishore[1] · Vikas Majithia[1]

Published online: 21 May 2019

Abstract

Purpose of Review Immunotherapy with immune checkpoint inhibitors (ICIs) has become a well-established modality to treat a number of different malignancies, especially in cases with advanced stages and/or recurrent diseases. These agents have been associated with development of a variety of autoimmune disorders as immune-related adverse events (IRAEs or irAEs). This review focuses on development of vasculitis with use of ICI.

Recent Findings Available information on vasculitis associated with immune checkpoint inhibition is limited primarily to case reports at this time. Most immune-related adverse events will not present as vasculitis, and it is an uncommon manifestation and/or is under-reported. There are no current well-established guidelines for treating vasculitis associated with ICIs; initial management would usually start with consideration of discontinuing the ICI and administering corticosteroids. Collaboration between treating oncologists and rheumatologists is necessary for a combined approach to management.

Summary While arthralgias, myalgias, and inflammatory arthritis frequently occur as irAEs, vasculitis is an uncommon presentation. Vasculitis has been reported with all of the available ICI agents, and there seems to be no clear difference in the risk based on small numbers. Large vessel vasculitis and vasculitis of the nervous system were the most commonly reported types of vasculitis but cases of vasculitis involving medium and small vessels have also been reported. It is challenging to know if the underlying disease or ICIs are the main culprit in development of vasculitis and requires a collaborative relationship between the treating oncologist and rheumatologist. Except in very mild cases, development of vasculitis during ICI therapy requires temporary or permanent discontinuation of ICI.

Keywords Immune check point inhibitors · Immune check point deficiency · Vasculitides/vasculitis · Chemotherapy · Malignancy · Cancer analysis · Review

Introduction

In the last decade, immunotherapy with immune checkpoint inhibitors has revolutionized the treatment of a variety of cancers. It is considered to be one of the most important advances in cancer treatment as it can be used for a number of different malignancies in various stages and has been especially effective in advanced, recurrent, and metastatic malignancies. However, this has also led to a new category of chemotherapy-associated immune-related adverse events (IRAEs or irAEs), primarily presenting as a number of autoimmune or inflammatory disorders. As of October 2018, there have been more than 200 reports of these irAEs, manifesting as rheumatoid arthritis, psoriatic arthritis, psoriasis, polymyalgia rheumatica (PMR), colitis, autoimmune hypophysitis, inflammatory arthritis, spondyloarthritis, sicca syndrome, myositis, myocarditis,

This article is part of the Topical Collection on *Vasculitis*

✉ Teresa M Crout
tcrout@umc.edu

Day S Lennep
dslennep@umc.edu

Shweta Kishore
skishore@umc.edu

Vikas Majithia
vmajithia@umc.edu

[1] Division of Rheumatology, University of Mississippi Medical Center, 2500 N State St., Jackson, MS 39216, USA

rhabdomyolysis, and vasculitis. This review focuses on one of the important consequences of these irAEs, vasculitis, and related disorders.

Background

Cancer immunotherapy is also referred to as "onco-immunotherapy" and utilizes immune checkpoint inhibitors (ICIs), which frequently block cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 pathways, programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1). This leads to purposeful immune dysregulation, thereby allowing patients to develop self-generated immune responses to cancer cells and control of the disease [1, 2]. Currently available agents to block these pathways are ipilimumab, nivolumab, pembrolizumab, and atezolizumab [1]. It is important to note that development of these irAEs can be a positive sign that these agents are being effective in the treatment of the primary malignancy and should be managed without interrupting the treatment if possible [3–5]. Rheumatologists sit at the forefront of this dilemma and are frequently asked to make difficult decisions in these circumstances. Hence, a working knowledge of these irAEs and their management is imperative for everyone learning and practicing rheumatology [4, 5].

Epidemiology/Scope of Issue

Rheumatic irAEs (rh-irAEs) appear to be less common than other irAEs, but this may be underestimated secondary to underreporting and heterogeneous presentations. Various types of rh-irAEs exist and prevalence is estimated to be roughly 1% to 10% [6•]. Of the rh-irAEs, vasculitis is less commonly reported and tends to occur later than other rh-irAEs. The majority of these cases are related to anti-CTLA-4 ipilumumab, followed by anti-PD1 pembrolizumab and nivolumab. The median duration from the initiation of immune checkpoint inhibition to the onset of irAEs was 3 months [7••]. Several types of vasculitis have been reported as rh-irAEs and range from single organ involvement to small, medium, and large vessel involvement. Of the reported cases, the types of vasculitides included giant cell arteritis (GCA), retinal vasculitis, uterine limited, primary angiitis of the central nervous system (PACNS), granulomatosis with polyangiitis (GPA), periaortitis, vasculitic neuropathy, cryoglobulinemic vasculitis, isolated aortitis, and digital vasculitis [7••]. Review of the literature shows that large vessel vasculitis and vasculitis of the nervous system were the most commonly reported types of vasculitis associated with immune checkpoint inhibition [7••].

Pathogenesis

The underlying mechanisms for why irAEs develop in the setting of immune checkpoint inhibition have yet to be revealed. It is likely related to the disruption of immunologic equilibrium provided by immune checkpoints [8]. There are several proposed mechanisms, including elevated levels of pre-existing autoantibodies, increasing T cell activity against antigens that are also present in healthy tissue, elevated cytokine levels, and heightened complement-mediated inflammation [8].

More recent data looking at the underlying pathogenesis of GCA may help us better understand the role immune checkpoint inhibition plays in the development of vasculitis. In GCA, it is theorized that the protective mechanism of immune checkpoints is disrupted, and there is a lack of expression of immunoinhibitory ligand PD-L1 in vessel wall dendritic cells. This leads to PD-1-positive CD4 T cells ability to enter the vessel wall and produce inflammatory cytokines, leading to vessel wall remodeling and eventually occlusion. This lack of PD-L1 promotes unopposed T cell–activating signals [9]. This is congruent with the finding mentioned previously that the most common type of vasculitis associated with immune checkpoint inhibition is large vessel vasculitis [7••].

Clinical Presentation and Features

Immune checkpoint inhibitors can cause adverse effects in multiple organs ranging from the skin, lungs, and heart to the musculoskeletal, gastrointestinal, renal, nervous, pituitary, adrenal, thyroid or ocular systems [10••] (see Table 1). Any new symptom after starting these medications should warrant an index of suspicion that it might be drug-induced. One can see from the table the variety of rh-irAEs affecting different organ systems. There is very little information available specifically on vasculitis associated with ICIs, and to this point, it is primarily limited to case reports. A systematic review of the literature as of 2018 found 53 cases of vasculitis after ICI, 20 confirmed, with the most commonly reported as large vessel vasculitis (GCA, isolated aortitis) and vasculitis of the central and peripheral nervous system [7••]. The most common malignancy was melanoma and the mean age was 54 ± 12 years. There was no significant difference in sex. Ipilimumab ($N = 8$) was the most common ICI, then pembrolizumab ($N = 6$), nivolumab ($N = 5$), and a combination of anti-PD1/anti-PDL-1/anti-CTLA-4 antibodies ($N = 1$). The number of treatment cycles ranged from 1 to 15 before vasculitic irAEs developed. The median time from start of therapy to irAEs was 3 (1.2–6) months (Table 2).

Table 1 Immune checkpoint inhibitor adverse effects by organ system involvement

Dermatologic	Inflammatory dermatitis
	Bullous dermatoses
	SJS, TEN, acute generalized exanthematous pustulosis, DRESS/DIHS
Gastrointestinal	Colitis
	Hepatitis
Pulmonary	Pneumonitis
Endocrinologic	General: headache, vision changes, rapid heartbeat, increased sweating, fatigue, weakness, myalgia, weight changes, dizziness, fainting, increased hunger/thirst, hair loss, deeper voice
	Primary hypothyroidism
	Hyperthyroidism
	Primary adrenal insufficiency
	Pituitary hypophysitis
	Diabetes
Musculoskeletal	Inflammatory arthritis
	Myositis
	Polymyalgia-like syndrome
Renal	Nephritis
Neurologic	Myasthenia Gravis
	Guillain-Barre syndrome
	Peripheral neuropathy
	Autonomic neuropathy
	Aseptic meningitis
	Encephalitis
	Transverse myelitis
Hematologic	Autoimmune hemolytic anemia
	Acquired thrombotic thrombocytopenic purpura
	Hemolytic uremic syndrome
	Aplastic anemia
	Lymphopenia
	Immune thrombocytopenia
	Acquired hemophilia
Cardiovascular	Myocarditis, pericarditis, arrhythmias, depressed ventricular function/heart failure, vasculitis
	Venous thromboembolism
Ocular	Uveitis/iritis
	Episcleritis
	Blepharitis

STS (Stevens-johnson syndrome), TEN (toxic epidermal necrolysis), DRESS (drugrash with eosihophilia and systemic symptoms, DIHS (drug induced hypersensitivity syndrome)

Confounding/Differentiating Factors From Other VASCULITIDES

From the beginning of the onset of ICI use, new adverse events have been reported and many of the rh-irAEs have had different phenotypes than the usual disease presentation. For example, the inflammatory arthritis after ICI use has had varying degrees of seropositivity with variation in large joint and small joint involvement [32]. The question which has been raised is: Is it the primary disease itself being unmasked, or is it due to the immunotherapy? The most obvious way to try to differentiate de novo vasculitis from a rh-irAE is the temporal relationship to the onset of vasculitis after the induction of ICI therapy.

One confounding factor is vasculitis as a paraneoplastic phenomenon. This type of vasculitis often resolves with chemotherapy or surgical resection of the tumor itself. This could be confused in a patient with a known malignancy receiving an ICI who then develops a vasculitis. One possible way to differentiate the two is if the vasculitis resolves with discontinuing the ICI, then it was likely drug-induced rather than paraneoplastic.

Evaluation and Diagnosis

The diagnosis is made based on the clinical presentation, laboratory tests, imaging studies, and, where indicated, a tissue biopsy of the involved organ such as the skin, nerve, or temporal artery biopsy. Given the overlapping presentation with other connective tissue disease and infections, it is imperative to exclude other etiologies and thus may require extensive investigations. Electromyography can confirm neuropathy; however, to determine the etiology, a nerve biopsy is often indicated. Early and accurate diagnosis is important to initiate the appropriate treatment to prevent long-term damage. A PET/CT may be required to rule out the recurrence of underlying malignancy as vasculitis can occur as a paraneoplastic phenomenon.

Table 3 lists the necessary clinical and laboratory investigations required to establish the diagnosis of immune-related vasculitis.

Differential Diagnosis

Paraneoplastic phenomenon causing polyarteritis nodosa (PAN), retinal vasculitis, GCA, leukocytoclastic vasculitis (LCV) due to melanoma or other cancers, and worsening metastatic disease are the most important differential diagnoses. Primary GCA, PMR, LCV, and connective tissue disease–related vasculitis could also occur. Acrocyanosis or thromboembolism needs to be considered in isolated acral vasculitis. Other differentials to be considered include hepatitis B–associated polyarteritis nodosa, hepatitis C–associated cryoglobulinemia, human immunodeficiency virus (HIV), and other infection-associated vasculitis. Presence of c-ANCA or specific enzyme immunoassays such as MPO or PR3 warrants investigation for ANCA-associated vasculitis.

Table 2 Comparison of immune checkpoint inhibitor-related vasculitis

Reference	Vessel size	Diseases	ICI	Treatments given for irAEs
[11–16]	Large	PMR/GCA Periaortitis Isolated aortitis "Large vessel vasculitis"	Ipilimumab Nivolumab Pembrolizumab	Discontinue (D/C) ICI IV CS (corticosteroids) Oral CS
[17–21]	Medium	Lymphocytic vasculitis of uterine/ovarian vessels Isolated vasculitis of PNS Vasculitic neuropathy: polyneuropathy with endoneural vasculitis type, asymmetric type Granulomatous vasculitis	Ipilimumab Nivolumab Pembrolizumab	D/C ICI IV CS pulse dose Oral CS
[22–27, 36]	Small	Retinal vasculitis GPA Digital vasculitis	Ipilimumab Nivolumab Pembrolizumab Tremelimumab Durvalumab Unknown Anti-PD1/PDL1 combo with anti-CTLA-4	D/C ICI Prednisolone ophthalmic drops Vitrectomy IV CS Oral cyclophosphamide Oral CS Epoprostenol Calcium channel blocker Nitropaste Botulinum toxin Sildenafil Rituximab Digital amputation Iloprost Acetylsalicylic acid Prostacyclin
[28–31]	Single organ	PACNS	Nivolumab Pembrolizumab	D/C ICI IV CS Oral CS

Based on literature search on or before 2/11/19

D/C discontinue, *ICI* (immune checkpoint inhibitor), *CS* corticosteroid, *PNS* peripheral nervous system, *GPA* granulomatosis with polyangiitis, *PACNS* primary angiitis of the central nervous system

Hypereosinophilia may indicate development of eosinophilic granulomatosis with polyangiitis.

Impact on Rheumatology

Although vasculitis seems to occur more seldom, it is associated with ICI treatment and requires prompt recognition by oncologists and referral to rheumatologists. As their use is increasing and many more new drugs for other cancers are in the pipeline, we expect to see many more patients developing immune-related vasculitis. The disease pattern can be heterogeneous and thus a high suspicion of these conditions is required. Rheumatologists need to be aware of ICI-associated PMR/GCA and other vasculitides and work with oncologists for further treatment. We also need to identify patients who may have an autoimmune susceptibility that is unmasked by ICI. Managing immune-related vasculitis is challenging due to the lack of evidence-based medicine or guidelines. The treatment approach for every patient is different based on the underlying malignancy and how immunosuppressive therapy may impact the cancer. One has to balance the risks and benefit of continuing ICI drugs and evaluate the need for immunosuppressive therapy.

Management

Managing these irAEs is a challenge for rheumatologists as standard guidelines cannot be applied, and there is a lack of evidence-based medicine. The American Society of Clinical Oncology has developed clinical practice guidelines to help manage patients affected by irAEs and help know when discontinuing the ICI is appropriate. Recommendations were designed based on a grading system for each irAE, from grade 1 to grade 4, and include several various adverse events.

Table 3 Evaluation of Suspected ICI-related vasculitis

Initial assessment
History and physical examination
Complete blood cell count with differential
Complete metabolic panel
Erythrocyte sedimentation rate
C-reactive protein
ANA
Rheumatoid factor
Anti-cyclic citrullinated peptide antibody
Cytoplasmic and perinuclear anti-neutrophil cytoplasmic antibodies
Enzyme immunoassay PR3, MPO
Cryoglobulin
Complement levels
Urinalysis
Beta-2 glycoprotein antibody
Anticardiolipin antibody
Coagulopathy panel
Hepatitis panel
HIV
Serum and urine electrophoresis
Biopsy of the affected organ such as skin, nerve, temporal artery
Other tests as indicated for assessment
Chest x-ray
Computerized tomography of chest
Nerve conduction study/electromyography
Arterial duplex Doppler
Angiogram
Transthoracic echocardiogram
Positron emission tomography

Unfortunately, vasculitis is not included in the recommendations and thus no specific definitions for grade 1 to grade 4 exist.

In general, grade 1 toxicities are closely monitored. Grade 2 toxicities may result in the need to hold the ICI and resume when symptoms and/or laboratory values revert to grade 1 or less. Prednisone 0.5 to 1 mg/kg/day may be administered. For grade 3 toxicities, holding the ICI is needed and high-dose corticosteroids at a dose of prednisone 1 to 2 mg/kg/day are initiated. The goal is to taper corticosteroids over the next 4 to 6 weeks. Infliximab may be offered if symptoms do not improve within 48 to 72 h of initiating high-dose corticosteroids. When symptoms and/or labs revert to grade 1 or less, rechallenging with the ICI can be done but caution should be used. For grade 4 toxicities, permanent discontinuation of the ICI is warranted [10••].

Of the reports of vasculitis, most cases achieved remission with either holding the ICI or administering glucocorticoids. Other reports have used hydroxychloroquine, rituximab, or cyclophosphamide in addition to glucocorticoid therapy [7••]. Based on the reports of treatment for other rheumatologic irAEs, other traditional disease-modifying anti-rheumatic drugs (DMARDs) can be considered.

Prognosis

The Journal of Clinical Oncology's management guidelines of irAEs states that management and treatment principles for vasculitis-induced irAEs are similar to those of other irAEs [10••]. It is not known if the prognosis is similar as well. Much of the information in regard to the prognosis of vasculitis-related irAEs is found in case reports. A systematic literature review found 20 confirmed cases of vasculitis associated with ICIs and all cases resolved with holding the ICI and/or administering corticosteroids [7••]. No patients died due to vasculitis. In 2018, Padda et al. reported perhaps the first case report of digital vasculitis after treatment with ipilimumab for metastatic melanoma [22]. After a course of high-dose corticosteroids, 5 days of epoprostenol and botulinum toxin, and four cycles of weekly rituximab 375 mg/m^2, it was felt that the progression of the ischemia was ceased; however, the patient did eventually require digital amputations about 6 months after symptom onset. Another case report published in 2018 describes a patient who developed digital vasculitis following treatment for metastatic urothelial bladder cancer with tremelimumab and durvalumab [23]. Oral corticosteroids provided significant improvement in this case. As discussed earlier, Richter et al. looked at retrospective data from 2011 to 2018 on rh-irAEs [6•]. Vasculitis was rarely reported and most of the patients developed inflammatory arthritis (2% prevalence). Of the patients with inflammatory arthritis, 3 were required to stop their ICI, 5 required a DMARD, and 76% were felt to need systemic corticosteroids. Vasculitis was grouped in with "other" rh-irAEs, and of these patients, 12% were required to stop their ICI while 71% needed further immunosuppression.

In regard to pre-existing autoimmune rheumatic disorders, these patients may be at higher risk of flaring their known disease or developing an irAE. One systematic review of 123 cases of ICI therapy in patients with pre-existing autoimmune disease showed that half of these patients developed a flare of their prior autoimmune disease, and the manifestation was generally the same as prior to ICI therapy [33]. Having a known autoimmune disease does not appear to be a contraindication to starting an ICI, however, and patients could even continue their ICI after the irAE was treated. A multicenter retrospective case series reported 30 patients with pre-existing autoimmune disease who received ipilimumab ICI therapy for melanoma; 25% of these patients had an exacerbation of their prior autoimmune disease and about 10% had a combination of de novo irAE and disease exacerbation [34, 35]. These adverse events also allow the researchers to study the

pathogenesis and various biomarkers during the development of vasculitis in a prospective manner which in the future may help us in identifying predisposed patients before starting immunotherapy.

Discussion and Future Direction

As highlighted in this article, ICI treatment is associated with a number of rheumatic manifestations. Even though there is a lack of reliable epidemiologic data, ICIs may be associated with up to 10% of the patients [1]. Among those, vasculitis is infrequent but can be quite serious and requires immediate action. The mildest variant of the vasculitides is PMR and can be easily managed by temporary discontinuation of the ICI or low-dose steroids. Thereafter, the next common forms of vasculitides are large vessel diseases and vasculitis of the central or peripheral nervous system. Other forms of vasculitides have been rarely reported and their exact prevalence remains unknown. The occurrence of vasculitis during ICI treatment would be categorized as a grade 3–4 adverse effect requiring discontinuation and additional therapy with steroids and/or immunosuppressive agents. All of the available ICI agents seem to be associated with vasculitis side effects and there does not seem to be a predilection with a single agent.

The rheumatic irAEs in ICI treatment emphasize the need for collaboration among rheumatologists and oncologists as well as continued learning for everyone about them as more data becomes available from these associations. There likely is going to be an explosion of these irAEs including vasculitides as ICIs possibly are used to treat limited cancer and/or new ICIs become available or they are used in combination therapy. More research is needed to determine the most effective and safe treatment. Drugs such as abatacept, a functional counterpart of ipilimumab, are already under trial for treatment of GPA.

Summary/Conclusions

Immune checkpoint–associated vasculitides remain rare but challenging rheumatic manifestations of these therapies. A collaborative relationship between oncologists and rheumatologists is the key to prompt recognition and appropriate management of these potentially life-threatening complications. Managing immune-related vasculitis remains challenging and should be individualized in each case.

Compliance With Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Sharon E, Streicher H, Goncalves P, Chen HX. Immune checkpoint inhibitors in clinical trials. Chin J Cancer. 2014;33:434–44.
2. Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. Nat Med. 2004;10:909–15.
3. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12:252–64.
4. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. JAMA Oncol. 2016;2:1346–53.
5. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. version 2. 2018. https://www.nccn.org/professionals/physician_gls/default.aspx.
6. • Richter MD, Crowson C, Kottschade LA, Finnes HD, Markovic SN, Thanarajasingam U. Rheumatic syndromes associated with immune-checkpoint inhibitors: a single-center cohort of 61 patients. Arthritis Rheum. 2019;71(3):468–75 **Rheumatic immune-related adverse effects from immune checkpoint inhibitors were examined retrospectively in a cohort of 61 patients in an effort to better understand the prevalence, presentation, and management of these patients. Although a small sample size, the study shows that vasculitis was less common compared with other Rh-irAEs.**
7. •• Daxini A, Cronin K, Sreih AG. Vasculitis associated with immune checkpoint inhibitors- a systematic review. Clin Rheumatol. 2018;37(9):2579–84 **This study reviewed the available literature on the cases of vasculitis in the setting of immune checkpoint inhibition. Each case of vasculitis was analyzed by type, presenting features, treatment, and outcome.**
8. Postow MA, Sidlow R, Hellman MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378:158–68.
9. Watanabe R, Zhang H, Berry G, Vaglio A, Goronzy JJ, Weyand CM. Immunoinhibitory checkpoint deficiency in medium and large vessel vasculitis. Am J Physiol Heart Circ Physiol. 2017;312(5):H1052–9.
10. •• Brahmer J, Lacchetti C, Schneider B, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 36:1714–68 **This systematic review looked at the toxicities associated with immune checkpoint inhibition and broke it down by organ system to provide awareness of the adverse effects as well as a clinical practice guideline for management of each type of toxicity.**
11. Goldstein BL, Gedmintas L, Todd DJ. Drug-associated polymyalgia rheumatic/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of CTLA-4. Arthritis Rheum. 2014;66:768–9.
12. Pinkston OFB, Wang B. Type and frequency of immune-related adverse reactions in patients treated with pembrolizumab (Keytruda), a monoclonal antibody directed against PD-1, in advanced melanoma at a single institution. [abstract]. Arthritis Rheum. 2016;68(sppl 10).

13. Abdel Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. PLoS One. 2016;11: e0160221.
14. Roy AK, Tathireddy HR, Roy M. Aftermath of induced inflammation: acute periaortitis due to nivolimumab therapy. BMJ Case Rep: 2017.
15. Cappelli LC, Shah AA, Bingham CO. Immune-related adverse effects of cancer immunotherapy- implications for rheumatology. Rheum Dis Clin N Am. 2017;43:65–78.
16. Ban BH Crowe J, Graham RM. Rheumatology case report immune-related aortitis associated with ipilimumab. The Rheumatologist 2017.
17. Minor DR, Bunker SR, Doyle J. Lymphocytic vasculitis of the uterus in a patient with melanoma receiving ipilimumab. J Clin Oncol. 2013;31:e356.
18. Liao B, Wang W, Hammack J, Mauermann M. Vasculitic neuropathy in the setting of nivolumab therapy for metastatic mesothelioma. Ann Neurol. 2016;80:M279.
19. Aya F, Ruiz-Esquide V, Vilado M, Font C, Prieto-Gonzalez S, Prat A, et al. Vasculitic neuropathy induced by pembrolizumab. Ann Oncol. 2017;28:433–4.
20. Arellano K, Mosley JC, Moore DC. Case report of ipilimumab-induced diffuse, nonnecrotizing granulomatous lymphadenitis and granulomatous vasculitis. J Pharm Pract. 2018;31:227–9.
21. Kao JC, Liao B, Markovic SN, Klein CJ, Naddaf E, Staff NP, et al. Neurological complications associated with anti-programmed death 1 (PD-1) antibodies. JAMA Neurol. 2017;74:1216–22.
22. Padda A, Schiopu E, Sovich J, Ma V, Alva A, Fecher L. Ipilimumab induced digital vasculitis. J immunother Cancer. 2018;6(1):12.
23. Comont T, Sibaud V, Mourey L, Cougoul P, Beyne-Rauzy O. Immune checkpoint inhibitor-related acral vasculitis. J Immunother Cancer. 2018;6(1):120.
24. Le Burel S, Champiat S, Routier E, Aspeslagh S, Albiges L, Szwebel T-A, et al. Onset of connective tissue disease following anti-PD1/PD-L1 cancer immunotherapy. Ann Rheum Dis. 2018;77:468–70.
25. Gambichler T, Strutzmann S, Tannapfel A, Susok L. Paraneoplastic acral vascular syndrome in a patient with metastatic melanoma under immune checkpoint blockade. BMC Cancer. 2017;17:327.
26. Manusow JS, Khoja L, Pesin N, Joshua AM, Mandelcorn ED. Retinal vasculitis and ocular vitreous metastasis following complete response to PD-1 inhibition in a patient with metastatic cutaneous melanoma. J Immunother Cancer. 2014;2:41.
27. Van Den Brom RR, Abdulahad WH, Rutgers A, Kroesen BJ, Roozendaal C, deGroot DJ, et al. Rapid granulomatosis with polyangiitis induced by immune checkpoint inhibition. Rheumatology (Oxford). 2016;55:1143–5.
28. Bender C, Dimitrakopoulou-Strauss A, Erik A, Hassel JC. Safety of the PD-1 antibody pembrolizumab in patients with high-grade adverse events under ipilimumab treatment. Ann Oncol. 2016;27: 1353–4.
29. Khoja L, Maruice C, Chappell M, MacMillan L, Al-Habeeb AS, Al-Faraidy N, et al. Eosinophilic fasciitis and acute encephalopathy toxicity from pembrolizumab treatment of a patient with metastatic melanoma. Cancer Immunol Res. 2016;4:175–8.
30. Laubli H, Hench J, Stanczak M, Heijnen I, Papachristofilou A, Frank S, et al. Cerebral vasculitis mimicking intracranial metastatic progression of lung cancer during PD-1 blockade. J Immunother Cancer. 2017;5:46.
31. Sun R, Danlos FX, Ammari S, Louvel G, Dhermain F, Champiat S, et al. Anti-PD-1 vasculitis of the central nervous system or radionecrosis? J Immunother Cancer. 2017;5:96.
32. Volansky, R. Checkpoint checkmate: adverse event management for checkpoint inhibitors. Healio Rheumatology. 12/2018.
33. Abdel-Wahab N, Shah M, Lopez-Olivio MA, et al. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. Ann Intern Med. 2017;168:121–30.
34. Suarez-Almazor ME, Kim ST, Abdel-Wahab N, Diab A. Immune-related adverse events with use of checkpoint inhibitors for immunotherapy of cancer. Arthritis Rheum. 2017;69(4):687–99.
35. Johnson DB, Sullivan RF, Ott PA, Carlino MS, Khushalani NI, Ye F, et al. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol. 2016;2: 234–40.
36. Le Burel S, Champiat S, Mateus C, Marabelle A, Michot JM, Robert C, et al. Prevalence of immune-related systemic adverse events in patients treated with anti-programmed cell death 1/anti-programmed cell death ligand-1 agents: a single-centre pharmacovigilance database analysis. Eur J Cancer. 2017;82:34–44.