CASE BASED REVIEW

Kaposi sarcoma in anti-neutrophil cytoplasmic antibody-associated vasculitis: a case-based review

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Received: 8 December 2020 / Accepted: 6 February 2021 / Published online: 23 February 2021
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Abstract
Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) are systemic necrotizing vasculitides associated with significant morbidity and mortality. Given the immunosuppression used to manage these conditions, it is important for clinicians to recognize complications, especially infectious ones, which may arise during treatment. Kaposi sarcoma (KS) is a lymphoangioproliferative neoplasm caused by human herpes virus 8 (HHV-8). Its cutaneous manifestations can mimic vasculitis. We describe a 77-year-old man with microscopic polyangiitis with pulmonary-renal syndrome treated with prednisone and intravenous cyclophosphamide who developed KS (HHV-8 positive) after 2 months of treatment. Cyclophosphamide was discontinued and prednisone gradually lowered with improvement and clinical stabilization of KS lesions. This comprehensive review includes all published cases of KS in patients with AAV, with a goal to summarize potential risk factors including the clinical characteristics of vasculitis, treatment and outcomes of patients with this rare complication of immunosuppressive therapy. We also expanded our literature review to KS in other forms of systemic vasculitis. Our case-based review emphasizes the importance of considering infectious complications of immunosuppressive therapy, especially glucocorticoids, and highlights the rare association of KS in systemic vasculitis.

Keywords Anti-neutrophil cytoplasmic antibody-associated vasculitis · Microscopic polyangiitis · Granulomatosis with polyangiitis · Kaposi sarcoma · Prednisone · Vasculitis

Introduction
Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) (Wegener’s), and eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome), all pauci-immune vasculitides which share clinical features and are characterized by the presence of ANCA [1]. Serious organ-threatening disease involvement with rapidly progressive glomerulonephritis, diffuse alveolar hemorrhage but also gastrointestinal, cardiac, and neurologic disease can occur [2]. The standard treatment for severe organ-threatening disease is glucocorticoids, followed by induction therapy with cyclophosphamide, or rituximab [3]. A serious consequence of immunosuppression is opportunistic infections. Kaposi sarcoma (KS) is a lymphoangioproliferative neoplasm that has been associated with human herpesvirus 8 (HHV8) [4–6]. Over the years, there have been four recognized types of KS: classic, endemic, iatrogenic (immunosuppression or transplant associated), and epidemic [4–6]. We report a case of hydralazine-induced AAV with pulmonary-renal syndrome complicated by iatrogenic KS during treatment. We performed a comprehensive search through MEDLINE using the following keywords: Kaposi sarcoma, vasculitis, ANCA vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis, Takayasu arteritis, polymyalgia rheumatica, giant cell arteritis, polyarteritis nodosa, and Behcet’s disease. We included articles published in English so that
developed a new lower extremity rash (Fig. 1a). Prednisone (400 mg/m²) infusion had been administered 2 weeks prior. The patient was increased from 40 to 45 mg by his local rheumatologist with some improvement. However, given persistent symptoms, the patient sought a second opinion at our tertiary care medical center. At the time of evaluation, he was on prednisone 45 mg daily and last cyclophosphamide (dose 2, 400 mg/m²) infusion had been administered 2 weeks prior. Apart from the rash, he denied any symptoms. Laboratory parameters, including renal function, were stable. Medication review revealed that he had been on treatment with hydralazine for hypertension for more than 1 year prior, and, given association of hydralazine with AAV, hydralazine was discontinued. Prednisone was lowered to 35 mg. Rituximab was discussed given severe manifestations of vasculitis but given positive hepatitis B core antibody, recommendation was made for evaluation with infectious diseases first. Unfortunately, 1 month later, he was hospitalized for mental status changes from urosepsis with Escherichia coli bacteremia. He was on prednisone 35 mg daily at the time. Treatment was complicated with Clostridium difficile colitis. During that hospitalization, further testing was pursued (Table 1). In addition, given lack of improvement in the lower extremity rash, a skin biopsy was obtained from his left thigh and his left foot. This showed an atypical HHV8-positive vascular proliferation without vasculitis consistent with KS (Fig. 1b–d). Testing for human immunodeficiency virus (HIV) was negative. While the initial plan was to start treatment with rituximab based on the severity of the manifestations of vasculitis, given the numerous infectious complications and hospitalizations, along with the absence of any evidence of active vasculitis, the recommendation was to hold off on immunosuppressive therapy. Furthermore, given that there was suspicion of this being hydralazine-induced, it was felt discontinuation of the trigger may also help. After discussion with the different specialists, and the patient, the decision was made to gradually taper prednisone and monitor closely without additional immunosuppressive therapy. He was also referred to oncology for co-management. He did not have any clinical evidence of gastrointestinal mucosal involvement of his KS and was started on treatment with topical imiquimod cream 5%. Chemotherapy was not considered since the etiology of his KS was felt to be due to immunosuppression as well as his recent history of multiple infections, renal insufficiency, and, immunosuppression was being lowered. He remains on prednisone 10 mg daily with adequate control of vasculitis and improvement in skin lesions. He continues to follow with rheumatology and oncology. Since discontinuation of cyclophosphamide and lowering prednisone, hypogammaglobulinemia has resolved with immunoglobulin G of 825 mg/dL (range 600–1540 mg/dL). He has had no further infectious complications and his KS remains clinically indolent.

**Case presentation**

A 77-year-old man of Italian American descent was referred to us for evaluation of AAV. He presented to an outside facility with a 30-lb weight loss, cough, scant hemoptysis, and worsening dyspnea on exertion. Laboratory evaluation showed acute kidney injury with a creatinine of 2.58 mg/dL (baseline 1.0 mg/dL) and BUN of 30 mg/dL, acute anemia with hemoglobin 6.1 g/dL. During hospitalization, he developed rapidly progressive renal failure requiring initiation of hemodialysis, in addition to gross hemoptysis. Serologies included a positive anti-nuclear antibody (ANA 1:320), positive double-stranded DNA (dsDNA 1:40), p-ANCA of 1:1280, MPO 52 IU (> 1 IU positive), and negative antinuclear antibodies were not tested. Bronchoscopy confirmed diffuse alveolar hemorrhage. A kidney biopsy was done but was non-diagnostic, showing acute tubular necrosis and mild mesangial matrix expansion with 4 out of 13 glomeruli which were globally sclerotic with mild parenchymal scarring. The patient was treated for a diagnosis of MPA with pulse does steroids, seven sessions of plasmapheresis followed by intravenous cyclophosphamide 400 mg/m² during hospitalization. He was able to successfully come off hemodialysis after 1.5 weeks with a new baseline creatinine of 2 mg/dL. Four weeks later, he was treated with cycle 2 of intravenous cyclophosphamide 400 mg/m².

Approximately 2 months after starting treatment, he developed a new lower extremity rash (Fig. 1a). Prednisone was increased from 40 to 45 mg by his local rheumatologist with some improvement. However, given persistent symptoms, the patient sought a second opinion at our tertiary care medical center. At the time of evaluation, he was on prednisone 45 mg daily and last cyclophosphamide (dose 2, 400 mg/m²) infusion had been administered 2 weeks prior. Apart from the rash, he denied any symptoms. Laboratory parameters, including renal function, were stable. Medication review revealed that he had been on treatment with hydralazine for hypertension for more than 1 year prior, and, given association of hydralazine with AAV, hydralazine was discontinued. Prednisone was lowered to 35 mg. Rituximab was discussed given severe manifestations of vasculitis but given positive hepatitis B core antibody, recommendation was made for evaluation with infectious diseases first. Unfortunately, 1 month later, he was hospitalized for mental status changes from urosepsis with Escherichia coli bacteremia. He was on prednisone 35 mg daily at the time. Treatment was complicated with Clostridium difficile colitis. During that hospitalization, further testing was pursued (Table 1). In addition, given lack of improvement in the lower extremity rash, a skin biopsy was obtained from his left thigh and his left foot. This showed an atypical HHV8-positive vascular proliferation without vasculitis consistent with KS (Fig. 1b–d). Testing for human immunodeficiency virus (HIV) was negative. While the initial plan was to start treatment with rituximab based on the severity of the manifestations of vasculitis, given the numerous infectious complications and hospitalizations, along with the absence of any evidence of active vasculitis, the recommendation was to hold off on immunosuppressive therapy. Furthermore, given that there was suspicion of this being hydralazine-induced, it was felt discontinuation of the trigger may also help. After discussion with the different specialists, and the patient, the decision was made to gradually taper prednisone and monitor closely without additional immunosuppressive therapy. He was also referred to oncology for co-management. He did not have any clinical evidence of gastrointestinal mucosal involvement of his KS and was started on treatment with topical imiquimod cream 5%. Chemotherapy was not considered since the etiology of his KS was felt to be due to immunosuppression as well as his recent history of multiple infections, renal insufficiency, and, immunosuppression was being lowered. He remains on prednisone 10 mg daily with adequate control of vasculitis and improvement in skin lesions. He continues to follow with rheumatology and oncology. Since discontinuation of cyclophosphamide and lowering prednisone, hypogammaglobulinemia has resolved with immunoglobulin G of 825 mg/dL (range 600–1540 mg/dL). He has had no further infectious complications and his KS remains clinically indolent.

**Discussion**

We present a rare case of MPA, possibly hydralazine-induced, with pulmonary-renal syndrome complicated by the development of KS during treatment with systemic glucocorticoids and cyclophosphamide.

One of the unusual aspects of this case was the possibility of the manifestations of AAV being hydralazine-induced. Severe manifestations including pulmonary-renal syndrome have been described in hydralazine-induced vasculitis [7–12]. A clue to this entity is the serologic profile...
which often includes other antibodies often seen in systemic lupus erythematosus (which hydralazine can also induce) in addition to ANCA (usually p-ANCA, MPO) [12]. Other positive serologies that have been reported with hydralazine-induced vasculitis are ANA, anti-histone antibodies, positive dsDNA, hypocomplementemia and anti-phospholipid antibodies [9, 12]. Our patient also had positive ANA and low titer dsDNA at initial diagnosis. While other connective tissue disease serologies, complements and testing for anti-phospholipid antibodies was performed, anti-histone antibody was not tested. The possibility of hydralazine-induced vasculitis was missed and considered few months later when he was evaluated at our facility for a second opinion. In most cases of serious organ manifestations, even though hydralazine was thought to be the trigger, in addition to withdrawal of the offending medication, immunosuppressive therapy including glucocorticoids, cyclophosphamide or rituximab were used [7]. In our case, the management was complicated by numerous infectious complications including KS.

The risk factors for KS include infection with HHV8, HIV, and immunosuppression [4–6, 13–15]. Our patient best fits as an example of iatrogenic KS, which has been widely reported in immunosuppressed patients, including those with organ transplantation [5, 16]. Despite the wide-spread use of immunosuppressive medications in systemic rheumatic diseases, the incidence of KS remains high.

Table 1 Laboratory findings at initial diagnosis of microscopic polyangiitis (MPA), and, later when diagnosis of Kaposi Sarcoma (KS) was made

| Laboratory (reference range) | Value At initial diagnosis MPA | Value At diagnosis KS |
|-------------------------------|------------------------------|----------------------|
| WBC (4.16 – 9.95 × 10E3/uL)   | 11.5                         | 19.81                |
| Absolute Neutrophil Count (1.80 – 6.90 × 10E3/uL) | 9.8                          | 18.22                |
| Absolute Lymphocyte Count (1.30 – 3.40 × 10E3/uL) | 0.58                         | 0.68                 |
| Hemoglobin (13.5–17.1 g/dL)   | 6.1                          | 11.6                 |
| Platelet Count (143 – 398 × 10E3/uL) | 176                         | 259                 |
| Sedimentation Rate By Modified Westergren (< OR = 20 mm/h) | > 120                        | 97                   |
| C-Reactive Protein (< 0.8 mg/dL) | 28.9                        | 1.19                 |
| Urea Nitrogen (7–22 mg/dL)    | 48                           | 86                   |
| Creatinine (0.60–1.30 mg/dL)  | 2.58                         | 2.95                 |
| Calcium (8.6–10.4 mg/dL)      | 9.0                          | 8.2                  |
| Phosphorus (2.3–4.4 mg/dL)    | 3.3                          | 5.5                  |
| Total Protein (6.1–8.2 g/dL)  | 5.8                          | 5.9                  |
| Albumin (3.9–5.0 g/dL)        | 2.2                          | 3.1                  |
| Alkaline Phosphatase (37–113 U/L) | 43                          | 217                 |
| Aspartate Aminotransferase (13–47 U/L) | 28                          | 88                   |
| Alanine Aminotransferase (8–64 U/L) | 18                          | 58                   |
| Procalcitonin (<0.10 ug/L)    | 1.53                         | 8.30                 |
| Immunoglobulin G serum (nl 726–1521 ml/dL) | Not tested                  | 533                  |
| Immunoglobulin A serum (nl 87–426 ml/dL) | Not tested                  | 201                  |
| Immunoglobulin M serum (nl 44-277 ml/dL) | Not tested                  | 92                   |
| HIV                           | Negative                     | Negative             |
| dsDNA Ab                      | Positive, 1:40               | Negative             |
| C-ANCA (< 1:20 titer)         | Negative                     | Negative             |
| P-ANCA (< 1:20 titer)         | 1:1280                       | Negative             |
| Proteinase-3 Ab               | Negative                     | Negative             |
| Myeloperoxidase Ab            | 52 (> 1 positive)            | <20.0 (> 20 positive) |
| C3 (76–165 mg/dL)             | 126                          | 132                  |
| C4 (14–46 mg/dL)              | 34                           | 35                   |
| Urinalysis                    |                              |                      |
| Protein/Creatinine Ratio,Ur (0.0–0.4) | 0.82                        | 0.3                  |
| RBC per HPF (0–2 cells/HPF)   | > 20                         | 0                    |
| WBC per HPF (0–4 cells/HPF)   | 0–2                          | 0                    |
| Hyaline Casts (0–2/LPF /LPF)  | 0                            | 11–20                |
diseases including vasculitis, the association of KS is rare, indicating there are other risk factors at play [17, 18].

A review of the literature evaluating KS in AAV, identified 10 additional cases whose findings are summarized in Table 2 [19–28]. The majority of the reports (70%) are in patients with GPA, with two reports in MPA and one in EGPA (Table 2). Age range was from 46 to 78 years with 60% of the cases being in men (Table 2). Time to onset of KS lesions ranged from 6 weeks to 11 months (Table 2). One reported case in the literature described coincidental occurrence of KS and GPA with worsening KS during treatment [26]. In another report, KS lesion on an ear was noted 19 years after diagnosis but, unusually, this patient had been given several different inflammatory diagnoses over the years including polyarteritis nodosa, neurosarcoidosis and finally, GPA [19]. All patients were still on systemic glucocorticoids and intravenous methylprednisolone were administered in 80% reported cases (Table 2). Adjunctive immunosuppressive therapy in patients who developed KS included cyclophosphamide (9 cases), azathioprine (3 cases) and mycophenolate mofetil (1 case), likely reflecting commonly used treatments in AAV given most cases had pulmonary and renal manifestations (Table 2). In all except one case, cutaneous involvement from KS was present, most frequently on the trunk and extremities. One case reported isolated KS of the gastrointestinal tract in a patient with GPA [28]. HHV-8 was positive in 6 of 7 cases where the information was provided (Table 2). The majority of cases improved with reduction or withdrawal of immunosuppressive therapy, especially glucocorticoids (Table 2). In some cases, chemotherapy and radiation therapy were also used to treat KS (Table 2). The status of the vasculitis after lowering immunosuppressive therapy was variable with some cases of relapses (Table 2). The patient in this case also presented many management challenges. Though hydralazine was thought to be the likely trigger of vasculitis, given the severe manifestations with pulmonary-renal syndrome, treatment with rituximab was considered. However, the patient

Fig. 1  a Multiple violaceous, coalescent, nodular lesions on the foot and ankle. b Histologic sections of skin from biopsy of a thigh lesion show dermis filled with irregular, somewhat jagged blood-filled vascular spaces adhering to collagen bundles and surrounding native blood vessels (so-called ‘promontory sign’, see arrows). Hematoxylin and eosin, 200x. c Performed CD34 immunohistochemistry strongly highlights irregular, infiltrative vascular spaces. CD34 immunohistochemistry, 200x. d Performed HHV8 immunohistochemistry highlights tumor endothelial cell nuclei and confirms the diagnosis of Kaposi’s sarcoma. HHV8 immunohistochemistry, 200x
Table 2  Summary of literature review of ANCA-associated vasculitis with Kaposi sarcoma

| Author                  | Age, years/sex | Diagnosis                      | AAV Organ involvement                        | ANCA type              | Immunosuppression                                                                 | Time to onset of KS | Areas affected by KS         | HIV and HHV-8 status         | Treatment                                                                 | Outcome                                      |
|-------------------------|----------------|--------------------------------|----------------------------------------------|-------------------------|-----------------------------------------------------------------------------------|---------------------|---------------------------------|-------------------------------|------------------------------------------------------------------------------|---------------------------------------------|
| Our case                | 77/M           | Drug-associated MPA           | Pulmonary-renal syndrome                     | p-ANCA, MPO             | Glucocorticoids (IV followed by oral prednisone), IV cyclophosphamide             | 6 Weeks             | Skin lesions on upper and lower extremities | HIV negative, HHV-8 positive | Withdrawal of cyclophosphamide, lower prednisone, imiquimod topical therapy | Regression KS, vasculitis in remission |
| Fatma et al.[20]        | 72/F           | MPA                            | Pulmonary-renal syndrome                     | Positive p-ANCA, MPO    | Glucocorticoids (IV followed by oral prednisone), IV cyclophosphamide             | 5 Months            | Skin lesions on trunk, lower extremities, face, neck | HIV negative, HHV-8 positive | Withdrawal of immunosuppression                                              | Regression KS, relapse vasculitis with alveolar hemorrhage |
| Biricik et al. [27]     | 71/M           | MPA                            | Pulmonary-renal syndrome                     | p-ANCA positive; MPO/PR3 not tested | Glucocorticoids (IV followed by oral prednisone), IV cyclophosphamide             | 3 Months            | Skin lesions on lower extremities | HIV status not provided, HHV-8 positive | Decrease glucocorticoid dose, cyclophosphamide discontinued, radiation therapy | Regression KS, vasculitis status not provided |
| Erban and Sokas[21]     | 78/M           | GPA                            | Pulmonary-renal syndrome, chronic sinusitis, arthritis | Not tested              | Glucocorticoids (oral methylprednisolone), oral cyclophosphamide                  | 10 Weeks            | Skin lesions on trunk, upper and lower extremities | HIV negative, HHV-8 status not provided | Glucocorticoid discontinued, cyclophosphamide continued, proton beam radiation to the feet | Regression KS, death from cardiogenic shock during cardiac bypass procedure |
| Deschenes et al.[22]    | 54/M           | GPA                            | Sinusitis, cavitary pulmonary lesions         | c-ANCA, PR3             | Glucocorticoids (IV then oral prednisone), oral cyclophosphamide                  | 8 Weeks             | Skin lesions on trunk, upper and lower extremities | HIV negative, HHV-8 status not provided | Glucocorticoids tapered off, cyclophosphamide reduced then discontinued after 20 months | Regression KS, vasculitis in remission |
| Hoff and Rødevand[19]   | 46/M           | GPA                            | Cranial neuropathies, sinusitis, arthritis, lung nodules | Negative c-ANCA, p-ANCA MPO/PR3 not tested | Glucocorticoids, IV cyclophosphamide (stopped due adverse effects), methotrexate | ~ 19 Years          | Skin lesion on ear               | HIV and HHV-8 status not provided | None                                                                         | Died of bladder cancer, vasculitis improved |
| Author          | Age, years/sex | Diagnosis                  | AAV Organ involvement                                      | ANCA type                             | Immunosuppression                          | Time to onset of KS | Areas affected by KS                      | HIV and HHV-8 status | Treatment                                                                 | Outcome                                                                 |
|-----------------|----------------|----------------------------|------------------------------------------------------------|---------------------------------------|-------------------------------------------|---------------------|-------------------------------------------|----------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Bouattar et al. [23] | 50/F           | GPA                        | Glomerulonephritis, L nasal ulceration                     | c-ANCA positive; MPO and PR3 not tested | Glucocorticoids (IV followed by oral prednisone), IV cyclophosphamide | 18 Weeks            | Skin lesions on trunk, upper and lower extremities | HIV negative, HHV-8 positive | Discontinuation of cyclophosphamide, decrease glucocorticoid dose       | Regression KS followed by recurrence, worsening renal function requiring dialysis, death from DIC |
| Saxena et al. [25] | 66/F           | GPA                        | Not provided                                               | Not provided                          | Glucocorticoids (IV followed by oral prednisone), IV cyclophosphamide | 5 Months            | Skin lesions on trunk and upper and lower extremities | HIV status not provided, HHV-8 positive | Cyclophosphamide continued for another month then switched to azathioprine, prednisone gradually tapered, azathioprine stopped for worsening KS, IV doxorubicin | Regression KS, vasculitis in remission                                                   |
| Kılıç et al. [26] | 70/F           | GPA                        | Nasal septal perforation, glomerulonephritis, pulmonary nodules | c-ANCA positive; MPO/PR3 not tested | Glucocorticoids (IV followed by oral prednisone), IV cyclophosphamide | 0 (Present at diagnosis but worse at 12 weeks) | Skin lesions on left lower extremity | HIV negative, HHV-8 negative | Glucocorticoids decreased, cyclophosphamide discontinued, radiation therapy, systemic chemotherapy (treatment not specified) | Not provided                                                                 |
| Endo and Nagata [28] | 73/M           | GPA                        | Not provided                                               | Not provided                          | Glucocorticoids (IV followed by oral prednisolone), IV cyclophosphamide 4 cycles then azathioprine | 11 Months           | Gastrointestinal ulcerations (upper and lower tract) | HIV negative, HHV-8 positive | Corticosteroids tapered from 11 mg per day to 6 mg per day, azathioprine continued | Ulcerations and lesions improved, vasculitis in remission |
had positive hepatitis B core antibody and recommendation was to start prophylaxis prior to treatment. Meanwhile, he developed numerous infectious complications including urosepsis, *Clostridium difficile* requiring hospitalizations which delayed initiation of rituximab. Finally, he also developed infectious complication of KS from HHV-8. Given that there was no evidence of active vasculitis, that hydralazine which may have been a trigger was discontinued, and risks of further immunosuppression, decision was made to use glucocorticoid monotherapy, lower prednisone gradually monitor closely. He clinically improved with reduction in glucocorticoid doses, discontinuation of cyclophosphamide, and topical imiquimod. To date, there has been no recurrence of vasculitis which may be in part from the discontinuation of hydralazine.

Given the rarity of KS in AAV, we also extended our literature review to other forms of systemic vasculitis (Table 3). We found reports in giant cell arteritis (4 cases), Behcet’s disease (2 cases), polymyalgia rheumatica (3 cases), IgA vasculitis (previously Henoch-Schönlein purpura, 1 case), and cutaneous vasculitis (1 case) [17, 29–37]. In all cases, patients were on glucocorticoid therapy (Table 3). As in the case of patients with AAV, cutaneous involvement from KS was present, most frequently on the trunk and extremities. There was a case of systemic involvement with KS of the gastrointestinal tract in a patient with Behcet’s disease [34]. The majority of cases improved with reduction or withdrawal of immunosuppressive therapy, especially glucocorticoids, with some relapses of the underlying vasculitis in some cases (Table 3).

Both the cellular and humoral arms of the immune system have been implicated in the control of KS. Immunosuppression is a common theme noted in KS, whether due to innate problems of host immunity, or, due to factors that lead to induced immunosuppression [38]. For instance, the rate of KS in acquired immunodeficiency syndrome (AIDS) patients is inversely proportional to the CD4 count [38]. In non-AIDS associated KS, based on our review of the literature, in patients with rheumatic conditions, glucocorticoids appear to be a consistent risk factor for KS irrespective of other immunosuppressive therapy [39]. Several potential mechanisms have been proposed to explain the association of KS from immunosuppression, including higher expression of chemokine receptors and growth factors, or culprit viral genes. However the data is limited and information is extrapolated from the post-transplantation KS literature [40]. Other possibilities could be the effects of glucocorticoids on lymphocyte depletion [22]. Some studies have found a direct effect of glucocorticoids in stimulating the development and growth of KS [41, 42]. Exogenous glucocorticoids can stimulate the proliferation of spindle cells in KS by upregulation of glucocorticoid receptors [41, 42]. They can also cause direct activation of HHV-8 [41, 42].

| Author | Age, years/sex | Diagnosis | AAV Organ involvement | ANCA type | Immunosuppression | Time to onset of KS | Areas affected by KS | HIV and HHV-8 status | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Berti et al. [24] | 67/M | EGPA, GPA | Glomerulonephritis, sinusitis, asthma, nasal polyposis | Not provided | Glucocorticoids (oral), mycophenolate mofetil | Not provided | Cutaneous HHV-8-negative, positive | HIV negative, HHV-8-positive | Mycophenolate mofetil was discontinued, prednisone continued (5 mg per day) | Regression KS, vasculitis in remission |

AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis, ANCA, anti-neutrophil cytoplasmic antibody, EGPA, eosinophilic granulomatosis with polyangiitis, GPA, granulomatosis with polyangiitis, HHS, human herpes virus 8, HIV, human immunodeficiency virus, IV, intravenous, KS, Kaposi sarcoma, M, male, MPA, microscopic polyangiitis, MPO, myeloperoxidase, PR3, Proteinase 3.
| Author          | Age, years/Sex | Diagnosis               | Immunosuppression             | Time to onset of KS | Areas affected by KS                      | HIV and HHV8 status                | Treatment                      | Outcome                                      |
|-----------------|----------------|-------------------------|-------------------------------|---------------------|-------------------------------------------|-----------------------------------|-------------------------------|---------------------------------------------|
| Klepp et al. [17] | 79/F            | Polymyalgia rheumatica  | Glucocorticoids (oral prednisone) | 7 Months            | Skin lesions lower extremities and eyelid | HIV status not provided, HHV-8 status not provided | Radiotherapy                  | Regression of KS, patient died suddenly of unknown cause |
| Vincent et al. [33] | 84/F            | Polymyalgia rheumatica  | Glucocorticoids (oral prednisone) | 4 Months            | Skin lesions on lower extremities         | HIV status not provided, HHV-8 positive | Not provided                 | Not provided                              |
| Brambilla et al. [37] | 72/F            | Polymyalgia rheumatica  | Glucocorticoids (oral prednisone) | 4 Years (was on 4 mg daily for 4 years) | Skin lesions on trunk, upper and lower extremities, leg lymphedema | HIV negative, HHV-8 positive | Gradually discontinue prednisone, taxol | Partial regression of KS, developed Merkel cell carcinoma requiring additional treatment |
| Leung et al. [29] | 70/F            | Giant cell arteritis    | Glucocorticoids (oral prednisone) | 5 Months            | Skin lesions upper and lower extremities, neck, lips, back | HIV status not provided, HHV-8 status not provided | Decrease in prednisone doses | Regression of KS, no flares of giant cell arteritis |
| Di Giacomo et al. [30] | 69/M            | Giant cell arteritis    | Glucocorticoids (oral prednisone) | 3 Months            | Skin lesions lower extremities            | HIV status not provided, HHV-8 status not provided | Decrease in prednisone, change to methyl-fluorodecortisolone | Status of KS not available, flare of giant cell arteritis |
| Soria et al. [32] | 45/F            | Giant cell arteritis    | Glucocorticoids (oral prednisone) | 3 Years            | Skin lesions upper and lower extremities, face, trunk | HIV status not provided, HHV-8 status not provided | Decrease in prednisone, vincristine, radiation therapy | Regression of KS, status of giant cell arteritis not provided |
| Kuttikat et al. [35] | 79/F            | Giant cell arteritis    | Glucocorticoids (oral prednisolone) | 6 Weeks            | Skin lesions on trunk, lower extremities | HIV negative, HHV-8 positive | Taper of prednisone with discontinuation | Resolution of KS, no flares of giant cell arteritis |
| Kotter et al. [34] | 29/M            | Behcet’s disease        | Glucocorticoids (oral prednisolone), cyclosporine A, azathioprine | 3 Years            | Skin, gastric mucosa, hard palate, pulmonary | HIV negative, HHV-8 positive | Discontinuation of azathioprine and cyclosporine A, taper prednisolone | Ocular disease flared requiring treatment with interferon alpha, both diseases in remission |
| Mezalek et al. [36] | 44/M            | Behcet’s disease        | Glucocorticoids (IV followed by oral prednisolone, IV cyclophosphamide × 6 then azathioprine) | 10 Months          | Skin lesions on lower extremities         | HIV negative, HHV-8 positive | Discontinuation of azathioprine, decrease glucocorticoid dose | Ocular disease flared requiring treatment with interferon alpha, both diseases in remission |
Finally, B-cells are latent reservoirs of HHV-8 [6]. While all reported cases of KS in AAV to date have been in patients treated with cyclophosphamide, azathioprine or mycophenolate mofetil, how the increased use of rituximab will affect risk of KS in AAV remains unclear. A recent report included 5 patients who developed KS after treatment with rituximab for their autoimmune conditions (none with AAV) [43]. All were on treatment with glucocorticoids (prednisone dose 10 mg to 35 mg). Time from rituximab to HHV-8 ranged from 3 to 11 months. Four of 5 patients had cutaneous manifestations but gastrointestinal, lung, urogenital disease, pleural effusion and lymphoma were also reported [43]. Two patients required treatment with radiation or chemotherapy [43].

In summary, despite immunosuppression in vasculitis, KS appears to be a rare complication of therapy. It is important to recognize KS as an infectious complication in patients with AAV. The violaceous, nodular lesions in KS, can be mistaken for the palpable purpura from cutaneous vasculitis which also affect the upper and lower extremities [44]. The majority of the cases were within the first year of treatment and the skin was the most frequently affected organ in KS. Glucocorticoid therapy appears to be an important risk factor. Lowering immunosuppression, especially glucocorticoids appears to be beneficial in causing regression of KS. However, this can be challenging since decreasing immunosuppression to help KS could potentially result in recurrence of the underlying systemic vasculitis. A multi-disciplinary approach is important along with individualizing the decision to lower immunosuppression with the possibility of relapse of vasculitis.

Author contributions All of the authors made contributions to the content of this article. The literature review and initial draft of the manuscript were prepared by BT and TK. Clinical and histopathologic images were provided by AS and GS. All authors commented on the manuscript. All authors read and approved the final manuscript as submitted and take full responsibility for all aspects of this manuscript.

Funding Not applicable.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflicts of interest/competing interests.

Consent for publication Consent for publication was obtained from the patient.

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