Malignancy risk in vasculitis

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***Abstract*:** The vasculitides encompass a rare subset of autoimmune diseases. Reports of the concurrent association of malignancies with some forms of vasculitis raise the possibility that patients with certain types of vasculitis may be at increased risk of cancer. Conversely, some forms of vasculitis may be a manifestation of malignancy. We review cancer risk in patients with large vessel vasculitis (giant cell arteritis and Takayasu arteritis), polyarteritis nodosa, and the circulating antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides. In addition we discuss vasculitis as a paraneoplastic phenomenon, highlighting polyarteritis nodosa in association with hairy cell leukemia and reviewing the most common vasculitic manifestation of cancer, cutaneous vasculitis.

***Keywords*:** cancer, cyclophosphamide, malignancy, paraneoplastic, vasculitis

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Introduction

The vasculitides comprise a group of heterogeneous autoimmune disorders with the common mechanism of disease involving inflammation of the blood vessels resulting in tissue ischemia with end-organ damage. There are many different forms of vasculitis, commonly classified based on the size of vessel involvement (Table 1) [Jennette *et al.* 1994]. The spectrum of clinical manifestations in vasculitis can range from localized single-organ involvement to life-threatening disease, with multiple major organs affected. In addition to the complex and varying disease manifestations that must be recognized and treated, clinicians must also be aware of the increased risk of malignancy that has been reported among certain forms of vasculitis [Faurschou *et al.* 2008; Knight *et al.* 2004, 2002; Pankhurst *et al.* 2004; Reinhold-Keller *et al.* 2000; Westman *et al.* 1998; Talar-Williams *et al.* 1996; Hoffman *et al.* 1992]. Clarification of the malignancy risk for the different types of vasculitis has prognostic implications for patients and may alter their clinical care, especially with respect to surveillance.

There are several potential mechanisms by which an increased malignancy risk may be associated with vasculitis. First, a dysfunctional immune system associated with autoimmunity may increase the risk of certain cancers [Weyand *et al.* 2006; Weyand and Goronzy, 2002]. Cytotoxic drug therapies used for the management of vasculitis, such as cyclophosphamide (CYC), may in turn modulate the subsequent risk of certain cancers [Emadi *et al.* 2009]. Vasculitis may be a paraneoplastic phenomenon as in the case of polyarteritis nodosa (PAN) with hairy cell leukemia (HCL) [Hasler *et al.* 1995]. Finally, a coincidental association related to detection bias (patients with vasculitis coming to medical attention and being followed more closely) may contribute to some reports of malignancy in association with vasculitis.

In this review, we provide an overview of the risk of cancer in the following systemic vasculitides: large vessel vasculitis (giant cell arteritis [GCA] and Takayasu arteritis [TAK]) systemic PAN, and the circulating antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (Churg–Strauss syndrome [CSS], microscopic polyangiitis [MPA], and Wegener's granulomatosis [WG]). While the risk of malignancy has been well studied in GCA, MPA, and WG, the evidence in the literature is more limited for PAN, TAK, and CSS. Where available, we focus on reports from case–control or cohort studies which address cancer risk or cancer-related mortality in vasculitis, rather than case reports where meaningful conclusions are difficult to reach. In the final section of this review, we discuss the association between PAN and HCL and review cutaneous vasculitis as a manifestation of malignancy.

Large vessel vasculitis

TAK and GCA are large vessel vasculitides which affect the aorta and its primary and secondary

Table 1. Classification of vasculitis by size of vessel involvement.

Large vessel
Takayasu arteritis
Giant cell arteritis
Medium vessel
Kawasaki disease
Polyarteritis nodosa
Small vessels
ANCA-associated vasculitis
Wegener's granulomatosis
Microscopic polyangiitis
Churg–Strauss syndrome
Henoch–Schönlein purpura
Cryoglobulinemic vasculitis
Cutaneous leukocytoclastic vasculitis

Adapted from Jennette *et al.* [1994]. ANCA, circulating antineutrophil cytoplasmic antibodies.

branches. While they share many clinical features, they also have several differences. TAK is a disease of predominantly young women while GCA affects the elderly and is exceedingly rare in individuals younger than age 50 years [Michel *et al.* 1996]. Malignancy risk has been well studied in GCA, but less so in TAK.

Takayasu arteritis

Aside from case reports, information on cancer in association with TAK is primarily available from cohort studies which have included cancer or cancer mortality as outcomes [Bicakcigil *et al.* 2009; Maksimowicz-McKinnon *et al.* 2007; Mwipatayi *et al.* 2005; Park *et al.* 2005; Vanoli *et al.* 2005; Jain *et al.* 1996; Ishikawa and Maetani, 1994; Kerr *et al.* 1994; Robles and Reyes, 1994; Zheng *et al.* 1992; Lupi-Herrera *et al.* 1977; Nakao *et al.* 1967]. In an Italian cohort of 104 patients with TAK, one patient was reported to have Hodgkin's lymphoma at diagnosis [Vanoli *et al.* 2005]. Only two cohort studies of patients with TAK, one from China [Zheng *et al.* 1992] and the other from Japan [Ishikawa and Maetani, 1994] evaluated mortality risk and reported mortality related to malignancies. In the Chinese cohort of 530 patients followed for a mean of 7.8 years, there was one death from stomach cancer [Zheng *et al.* 1992]. One patient in the Japanese cohort (120 patients with median follow up of 13 years) died from cervical cancer [Ishikawa and Maetani, 1994]. Few studies have addressed treatment-related cancer outcomes in TAK. In an NIH cohort study of treatment-related complications involving 60 patients with TAK, none of the five patients treated with CYC developed cancer over a median follow up of 5.3 years [Kerr *et al.* 1994]. In a single-center study of 25 patients treated with anti- tumor necrosis factor (TNF) therapies, one patient developed breast cancer which was thought to be related to exposure to infliximab [Molloy *et al.* 2008].

There have been no studies which have compared cancer risk in TAK to that of the general population or matched controls. Given the limited data on cancer risk in TAK, it is difficult to draw any meaningful conclusions. However, the evidence to date does not support an increased risk of malignancy in TAK. Further studies would be required to definitively address cancer risk in these patients.

Giant cell arteritis

Five studies have examined malignancy risk in GCA [Hill *et al.* 2010; Ji *et al.* 2010; Kermani *et al.* 2009; Myklebust *et al.* 2002; Haga *et al.* 1993]. All included a comparison group, which is important since GCA patients are older and may be at increased risk of cancer due to age. Three of the above studies included patients with polymyalgia rheumatica (PMR) in addition to subjects with GCA [Ji *et al.* 2010; Myklebust *et al.* 2002; Haga *et al.* 1993]. An additional study evaluated mortality in GCA patients with and without cancer without information on cancer risk and is not reviewed here [Gonzalez-Gay *et al.* 2007].

In a case–control study from Norway by Haga and colleagues evaluating cancer in 120 patients with PMR and 65 GCA patients, no overall increased cancer risk was noted. However, in a subgroup analysis of patients with GCA confirmed by temporal artery biopsy, cancer risk was statistically higher compared with controls (hazard ratio 2.35, 95% CI 1.03–5.34) [Haga *et al.* 1993]. A subsequent population-based case–control study from Norway involving 398 patients of whom 318 had PMR and 80 had GCA, found no increased risk of cancer in PMR or GCA. Furthermore, there was no increased risk of cancer even in the subset of GCA patients with a positive temporal artery biopsy. The authors suggested that the findings of the prior study by Haga and colleagues [Haga *et al.* 1993] may have been due to selection bias as they compared hospital-based cases with population-based controls [Myklebust *et al.* 2002]. In a population-based cohort study using an incident cohort of 204 GCA patients from Olmsted County, MN, USA, there was no

increased cancer risk in GCA patients compared to an age- and gender-matched referent cohort followed over a median of 7.7 years [Kermani *et al.* 2009]. In this study, there was a trend toward increased incident cancers in the first year following GCA diagnosis ($p = 0.09$), but this may have been related to detection bias [Kermani *et al.* 2009]. In addition, a study from Australia of 226 temporal artery biopsy-positive GCA patients also found no overall increased risk of cancer in GCA patients compared with the general population [Hill *et al.* 2010]. Finally, a recent study from Sweden evaluated cancer risk in PMR and GCA. This study included a large number of patients (35,928), but the subjects were identified using the Swedish Hospital Discharge Register. The investigators found GCA and PMR patients had a 19% excess in incidence of cancer (standardized incidence ratio 1.19; 95% CI 1.06–1.23). In subgroup analysis, most of the excess cancers were related to melanoma, squamous cell skin cancers, and leukemias. The authors of this study concluded that PMR and GCA patients are at marginally increased cancer risk [Ji *et al.* 2010]. However, when interpreting these findings, several factors need to be considered. First, the diagnosis of PMR or GCA was not confirmed by the investigators and therefore misclassification bias remains a concern, especially regarding the diagnosis of PMR where malignancies may mimic PMR symptoms. In addition, no information was provided on the proportion of subjects with PMR and GCA and therefore, it remains unclear whether the increased risk of malignancy was confined to subjects with PMR, GCA, or both.

While the data are somewhat conflicting, most studies have concluded that there does not appear to be an increased risk of incident cancer in GCA [Hill *et al.* 2010; Kermani *et al.* 2009; Myklebust *et al.* 2002]. Furthermore, even in the largest study which did report an increased risk of cancer, the risk was marginal and it was unclear whether the increased risk involved patients with GCA [Ji *et al.* 2010].

Polyarteritis nodosa

Polyarteritis nodosa is a systemic necrotizing vasculitis of primarily medium and occasionally small muscular arteries. Its association with hepatitis B (HBV) infection is well recognized. Based on a recent study, the incidence of HBV-associated PAN appears to be declining [Pagnoux *et al.* 2010]. There are few studies evaluating cancer risk in patients with PAN, with most information available from the French Vasculitis Study Group and their series of patients with PAN.

Three studies have evaluated cancer-related mortality and treatment-related cancers in patients with PAN [Pagnoux *et al.* 2010; Ribi *et al.* 2010; Guillevin *et al.* 2005]. In a series of 115 patients with HBV-associated PAN, three patients (2.6%) died from cancer over a mean follow-up of 69 months; two had lung cancer and one patient had prostate cancer. Both deaths occurred >15 months after diagnosis [Guillevin *et al.* 2005]. In a prospective, randomized, open-label treatment study that included 58 patients with non-HBV associated PAN, three PAN patients (5.2%) developed cancer over follow-up [Ribi *et al.* 2010] including one Hodgkin's lymphoma (randomized to azathioprine use) and two colon cancers (randomized to corticosteroids only). The cancers occurred 19 months, 10 months and 4 years, respectively, after inclusion in the study [Ribi *et al.* 2010]. Finally in a large cohort of 348 patients with PAN with mean follow up of 68.3 months, there were five cancer-related deaths (1.4%). This included one lung cancer, one liver cancer, two prostate cancers, and one myelodysplasia occurring 4–19 years after PAN diagnosis [Pagnoux *et al.* 2010]. Interestingly, a recent cohort study from Denmark evaluated risk of anal squamous cell carcinoma in conjunction with immunosuppressive disorders and included 1174 patients with PAN. This study found an increased standardized incidence ratio of anal cancer with PAN (SIR 8.8; 95% CI 1.5–29) [Sunesen *et al.* 2010]. However, as evident by the large confidence interval, the number of cases was small with only two cases of anal cancer among 1174 PAN patients [Sunesen *et al.* 2010].

Based on the available literature, development of cancer in patients with PAN appears rare. Furthermore, at present, the contributory role of medications in subsequent development of cancer remains unclear.

ANCA-associated vasculitis

Most studies on malignancy risk in ANCA-associated vasculitis have included either MPA or WG. One study evaluated long-term outcomes in 278 patients with PAN, MPA, and CSS [Gayraud *et al.* 2001]. In this study, there were

13 cancer-related deaths but no information is provided regarding overall incidence of cancer or the vasculitis type in the 13 patients who died from cancer [Gayraud *et al.* 2001]. There are no other studies evaluating cancer risk in CSS.

Several studies have consistently demonstrated an increased risk of cancer in WG [Faurschou *et al.* 2008; Knight *et al.* 2004, 2002; Pankhurst *et al.* 2004; Reinhold-Keller *et al.* 2000; Westman *et al.* 1998; Talar-Williams *et al.* 1996; Hoffman *et al.* 1992] and MPA [Pankhurst *et al.* 2004; Westman *et al.* 1998]. This risk appears in part to be related to cytotoxic medications used for treatment, especially CYC. CYC, a known carcinogen, is an alkylating agent, the active compound of which is phosphoramide mustard, which produces interstrand and intrastrand DNA crosslinks [Emadi *et al.* 2009]. CYC use has been associated with an increased risk for bladder cancer, acute leukemia, and skin cancer [Emadi *et al.* 2009], which are the same types of malignancies reported among patients with WG and MPA exposed to CYC.

CYC is an induction agent in the treatment of ANCA-associated vasculitis and studies have found increased risk of bladder cancer in WG and MPA [Faurschou *et al.* 2008; Knight *et al.* 2004, 2002; Pankhurst *et al.* 2004; Reinhold-Keller *et al.* 2000; Westman *et al.* 1998; Talar-Williams *et al.* 1996; Hoffman *et al.* 1992]. Risk of other cancers, particularly skin cancer and hematologic malignancies is also increased in these patients. In a cohort of 158 WG patients followed for a mean of 8 years, six patients developed cancer (four bladder and two lymphomas) [Hoffman *et al.* 1992]. There was a prolonged period of latency from CYC exposure to detection of bladder cancer ranging from 7 months to 12 years. The investigators compared the observed cancers to that expected for the general population using the National Cancer Institute Registry and found a 2.4-fold overall increase in cancer with a 33-fold increase in bladder cancer and 11-fold increase in lymphomas [Hoffman *et al.* 1992]. In a study evaluating bladder toxicity in 145 patients with WG treated with CYC, 7 patients (4.8%) developed bladder cancer [Talar-Williams *et al.* 1996]. Furthermore, incidence of bladder cancer increased with time, with an estimated incidence of 16% over 15 years after CYC exposure [Talar-Williams *et al.* 1996]. In another cohort of 155 patients with WG, followed for a median of 7 years, 7 patients (4.5%) developed cancer. In this study, a cumulative CYC dose of $\geq$100 g was associated with a twofold increased risk of cystitis or myelodysplastic syndrome compared with WG patients who received lower cumulative doses of CYC [Reinhold-Keller *et al.* 2000].

The results of three population-based studies [Faurschou *et al.* 2008; Knight *et al.* 2004, 2002] evaluating cancer incidence in WG are concordant with findings from cohort studies. In a population-based study from Sweden of 1065 patients with WG, there was a twofold overall increased risk of cancer compared with the general population [Knight *et al.* 2002]. The most pronounced increase was for bladder cancer, squamous cell skin cancer, and malignant lymphomas [Knight *et al.* 2002]. In a subsequent study [Knight *et al.* 2004], these investigators evaluated the effect of CYC treatment on subsequent development of bladder cancer. They found that WG patients with bladder cancer had received higher cumulative doses of CYC (median dose 113 g) compared with WG patients without bladder cancer (median dose 25 g) [Knight *et al.* 2004]. The median duration of CYC treatment was shorter in WG patients without bladder cancer [Knight *et al.* 2004]. The above two findings strongly suggest a dose-dependent risk of bladder cancer in WG. Another important finding was that the incidence of bladder cancer increased with duration of follow up [Knight *et al.* 2004]. In a population-based study of 293 WG patients in Denmark, there was an increased risk of bladder cancer, nonmelanoma skin cancers, and acute myelogenous leukemia [Faurschou *et al.* 2008]. In this study there was no excess of cancer in WG patients who never received CYC suggesting that the increased risk of malignancies observed is likely related to treatment with CYC. This study also tried to assess the effect of maintenance immunosuppressive treatment on subsequent cancer risk and found an increase in bladder cancer and nonmelanoma skin cancer in patients treated with CYC who were later switched to methotrexate or azathioprine compared with patients who never received maintenance treatment following CYC, however results did not reach statistical significance [Faurschou *et al.* 2008].

While all of the above studies included only WG, not surprisingly, the two studies evaluating

cancer risk in WG and MPA patients also found increased cancer risk [Faurschou *et al.* 2008; Knight *et al.* 2004, 2002; Pankhurst *et al.* 2004; Reinhold-Keller *et al.* 2000; Westman *et al.* 1998; Talar-Williams *et al.* 1996; Hoffman *et al.* 1992]. In a cohort of 123 patients with renal involvement from WG (56 patients) and MPA (67 patients), followed for a median 55 months, there was an increased risk of bladder cancer and skin cancer compared with the general population [Westman *et al.* 1998]. CYC treatment for at least 12 months was associated with an 11-fold increase of bladder cancer, while azathioprine use for at least 12 months and corticosteroid use for at least 48 months was associated with increased risk of skin cancer [Westman *et al.* 1998]. A study by Pankhurst and colleagues retrospectively evaluated prior or concurrent cancers in 200 patients with WG or MPA and found that compared with age-matched controls, cancer was increased in these patients [Pankhurst *et al.* 2004].

Finally, in the Wegener's Granulomatosis Etanercept Trial (WGET), 180 WG patients were randomized to either etanercept or placebo, in addition to receiving standard treatment with CYC or methotrexate. Etanercept was not effective in the maintenance of induction [WGET Group 2005]. However, 6 of 89 patients randomized to etanercept developed solid malignancies over a median follow up of 2 years compared with none of the 91 patients in the placebo group ($p = 0.01$). All patients who developed the solid tumors were also treated with CYC. These data suggest that the combination of CYC and anti-TNF therapy may augment the risk of cancer beyond what would be expected with CYC treatment alone [Stone *et al.* 2006]. A summary of the studies evaluating cancer risk following diagnosis of WG or MPA is available in Table 2.

The above studies enable us to make several important conclusions. First, in contrast to the other vasculitides, cancer risk is clearly increased in WG and MPA. Second, the increased risk appears to be related to CYC treatment with some studies suggesting a dose-dependent relationship. The highest risk is for bladder cancer but the risk of skin cancer, leukemias, and lymphomas is also increased. Disturbingly, there can be a long latency period between drug exposure and cancer detection. All of these findings suggest that whenever possible, attempts should be made to minimize cumulative CYC exposure. More importantly, these patients require long-term follow up to monitor for development of these complications. There continues to be a need for alternatives to CYC with less toxicity.

Vasculitis as a manifestation of cancer

In the preceding sections, we have reviewed the risk of cancer in different forms of vasculitis. In this section, we explore vasculitis as a clinical

Table 2. Summary of studies evaluating subsequent cancer risk in ANCA-associated vasculitis.

Study	Type of ANCA vasculitis	Patients with cancer (total number of patients)	Summary of findings	Types of cancer
Hoffman *et al.* [1992]	WG	6 (158)	Overall increased risk of cancer	Bladder cancer, lymphomas
Talar-Williams *et al.* [1996]	WG	7 (145)	Increased risk of bladder cancer	Only evaluated bladder cancer
Knight *et al.* [2002]	WG	110 (1065)	Overall increased risk of cancer	Bladder cancer, squamous cell skin cancer, leukemia, lymphoma, and liver cancer
Faurschou *et al.* [2008]	WG	50 (293)	Overall increased risk of cancer	Bladder cancer, acute myeloid leukemia, non-melanoma skin cancer
Westman *et al.* [1998]	WG and MPA	15 (123)	Increased risk of bladder and skin cancer	Bladder cancer, skin cancer
WGET Group [2005]	WG and MPA	6 (180)	Increased risk cancer in etanercept group patients who also received CYC compared to placebo group	Solid malignancies

ANCA, anti-neutrophil cytoplasmic antibodies; WG, Wegener's granulomatosis; MPA, microscopic polyangiitis; CYC, cyclophosphamide.

manifestation of an underlying malignancy. Although rare, vasculitis and cancer may occur concurrently. While the mechanisms by which cancer could result in manifestations of vasculitis are not clearly understood, numerous hypotheses have been suggested. These include impaired clearance of immune complexes, immunogenicity related to cancer antigens which may share homology to vascular antigens, or an immunologic response to either deposition of neoantigens or alteration of self-antigens in vessel walls [Hutson and Hoffman, 2000].

Hairy cell leukemia and polyarteritis nodosa

There is a well-recognized association between HCL and PAN [Fortin, 1996]. HCL is a rare, B-cell lymphoproliferative disorder which can manifest as paraneoplastic vasculitis, either a leukocytoclastic vasculitis or PAN. Both HCL and PAN are rare diseases and their concurrent association exceeds what would be expected by chance alone [Hasler *et al.* 1995]. Furthermore, there is direct evidence linking the two conditions with histopathology showing direct invasion of the vessel wall by leukemic cells [Hasler *et al.* 1995]. In a literature review of 42 cases of vasculitis associated with HCL, 21 cases were consistent with PAN (with four cases demonstrating vessel wall infiltration by the leukemic cells). PAN often occurred after the diagnosis of HCL and splenectomy. The vasculitis caused by HCL may be indistinguishable from PAN but may present with unusual features such as involvement of the temporal arteries or cerebral arteries [Fortin, 1996; Hasler *et al.* 1995; Gabriel *et al.* 1986]. While both diseases are rare and the mechanisms of vasculitis in HCL are not well understood, clinicians need to be aware of this association.

Cutaneous vasculitis

Another important vasculitic manifestation of cancer is cutaneous vasculitis. In all studies evaluating series of patients with vasculitis and cancer, cutaneous vasculitis was the most common vasculitis in association with cancer. In some studies, the two were concurrent (within 1 year). In addition, in some cases, the course of vasculitis was atypical in its refractory nature to immunosuppressive therapy and instead, responded to treatment towards the underlying malignancy suggesting a true paraneoplastic association.

In a study by Greer and colleagues spanning 17 years at a single institution, 13 patients with a hematologic disorders (myeloproliferative or lymphoproliferative) were identified as having vasculitis [Greer *et al.* 1988]. All had a cutaneous vasculitis with skin biopsies showing evidence of small-vessel and leukocytoclastic vasculitis [Greer *et al.* 1988]. In 10 patients, the cutaneous vasculitis preceded cancer by an interval of 1–38 months. While the study by Greer and colleagues focused on hematologic malignancies, both solid and hematologic cancers have been reported with cutaneous vasculitis [Fain *et al.* 2007; Hutson and Hoffman, 2000; Garcia-Porrua and Gonzalez-Gay, 1998]. In a case series of 11 patients with cancer and vasculitis, 9 patients had cutaneous vasculitis with solid malignancies in 4 cases [Sanchez-Guerrero *et al.* 1990]. In a review of 2800 vasculitis patients seen over an 18.5 year period at the Cleveland Clinic, 12 patients (0.4%) were diagnosed with vasculitis and cancer within the same 1 year period [Hutson and Hoffman, 2000]. Half of the patients had a solid malignancy. The most common vasculitis was cutaneous leukocytoclastic vasculitis (7 of 12 cases) [Hutson and Hoffman, 2000]. Interestingly, there was clinical concordance between disease activity and treatment response for cancer and vasculitis in 8 of 10 patients with follow up [Hutson and Hoffman, 2000]. For example, there were cases of leukocytoclastic vasculitis (usually very steroid responsive) that did not respond to high-dose prednisone but improved once treatment was initiated for the underlying cancer [Hutson and Hoffman, 2000]. This concordance in clinical course has also been reported by Solans-Laque and colleagues [Solans-Laque *et al.* 2008]. In their study, which included 15 patients with vasculitis (60% leukocytoclastic vasculitis) and concurrent solid malignancy (within 1 year), there were cases where treatment of cancer resulted in resolution of vasculitis. More intriguingly, in half the patients, recurrence of vasculitis was associated with tumor recurrence [Solans-Laque *et al.* 2008]. Finally, Fain and colleagues evaluated 60 patients with vasculitis and malignancy, 22 (36.7%) of whom developed both diseases within 1 year [Fain *et al.* 2007]. As in other studies evaluating cancer and vasculitis, the most common vasculitis was cutaneous leukocytoclastic vasculitis (45% cases). In this study, hematologic cancers were most commonly associated with vasculitis (63% cases) [Fain *et al.* 2007].

Two studies have assessed the prevalence of cancer in patients with cutaneous vasculitis

[Garcia-Porrua and Gonzalez-Gay, 1998; Jessop, 1995]. Among 69 patients with cutaneous leukocytoclastic vasculitis, 3 patients (4.3%) had malignancy as a potential etiologic agent of the vasculitis including one bronchial carcinoma and two lymphoproliferative malignancies [Jessop, 1995]. Similarly, of 192 patients with small-vessel cutaneous vasculitis, 8 patients (4.2%) had cancer with hematologic cancers being the most common neoplasm [Garcia-Porrua and Gonzalez-Gay, 1998]. Therefore, even though cutaneous vasculitis is the most common vasculitis associated with cancers, the prevalence of cancer in patients with cutaneous vasculitis is low.

There is an association between HCL and PAN. Clinically, the manifestations of PAN from HCL is indistinguishable from the idiopathic form but involvement of arteries such as temporal arteries and cerebral arteries which are atypical for idiopathic PAN may provide clues to a paraneoplastic phenomenon. Although large, medium, and other small vessel vasculitides have been reported in association with malignancy in several series [Solans-Laque *et al.* 2008; Fain *et al.* 2007; Hutson and Hoffman, 2000; Sanchez-Guerrero *et al.* 1990], cutaneous vasculitis appears to be the most common vasculitic manifestation of cancer. The pathophysiologic mechanisms for the preferred vessel size (small vessel) involvement or the reasons why the primary manifestation is most often cutaneous as opposed to renal or pulmonary are not well understood. Both solid and hematologic malignancies have been associated with cutaneous vasculitis. Screening all patients with cutaneous vasculitis for a malignancy would not be cost effective or warranted, but rather emphasis should be placed on the history, physical examination, and clinical course of the disease. Malignancy should be suspected in cases where cutaneous vasculitis does not respond appropriately to corticosteroids or when it is refractory to treatment. Atypical clinical features such as profound weight loss or other constitutional symptoms with isolated cutaneous vasculitis should prompt further investigations. In addition, isolated cutaneous vasculitis in a patient with a known history of a treated malignancy should raise concern of recurrence of the cancer. In evaluating patients with suspected paraneoplastic vasculitis, the physician should ensure that the patients are up to date with age-appropriate cancer screening. Additional testing including imaging studies may be warranted but should be directed based on history, clinical examination and laboratory findings.

Conclusions

Awareness by clinicians of cancer risk among the different types of vasculitis is important for the initial evaluation and subsequent follow up of these patients. Furthermore, there are obvious prognostic implications for patients with WG and MPA where an increased risk of cancer is most consistently observed. Based on our review, there does not appear to be an increased association of cancer in either TAK or PAN, but the evidence in the literature is limited. Most studies in GCA did not demonstrate any increased cancer risk following diagnosis. In contrast, there is an increased risk for cancer in WG and MPA, specifically for bladder, skin, and hematologic malignancies, and this risk appears to be associated with CYC use, particularly higher cumulative doses. Patients exposed to CYC require close follow up given the prolonged latency in some cases between drug exposure and identification of cancer. Finally, HCL can mimic PAN while cutaneous vasculitis may be a common manifestation of both solid and hematologic malignancies. Further study on this observed association between malignancies and the development of some forms of vasculitis may serve to enhance our understanding on the complex interplay between the immune system and blood vessels in the pathogenesis of vasculitis.

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Conflict of interest statement

None declared.

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