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Vasculitis in the Geriatric Population

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Vasculitis is histologically defined by the presence of blood vessel inflammation. As a result of this vascular inflammation, stenoses may develop with subsequent tissue ischemia, or there may be attenuation of the vessel wall leading to aneurysm formation or hemorrhage. Vasculitis can occur as a primary disease entity in which no currently identified cause has been identified or secondary to an underlying disease or exposure.

Patient age can play a very important role in many different facets of vasculitic disease. The most common form of systemic vasculitis seen in humans, giant cell arteritis, occurs almost exclusively in people older than 50 years. For this and many other forms of vasculitic disease that can develop in older patients, the challenges of diagnosis and treatment can be compounded further by the presence of comorbid diseases and concomitant medications.

This article seeks to review the vasculitic diseases that may be most frequently encountered in patients older than 65 as well as management issues that warrant special consideration in geriatric vasculitis patients.

Vasculitic disease in patients over age 65

Primary vasculitic diseases

The first account of a primary systemic vasculitic disease was made in 1866 when Kussmaul and Maier [1] described a disease process characterized by nodular inflammation of the muscular arteries that they named *periarteritis nodosa* (later referred to as *polyarteritis nodosa* [PAN]). During the 1900s the description of clinical entities associated with vasculitis emerged, and in 1952, Zeek [2] proposed the first classification system for the vasculitic

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diseases. Since that time, the nomenclature and classification of the vasculitides has continued to evolve. One means of categorizing the vasculitic diseases is based on the predominant size of blood vessel involvement [3,4].

Large vessel vasculitis

Giant cell arteritis and polymyalgia rheumatica

Giant cell arteritis (GCA), also called *temporal arteritis*, is a granulomatous arteritis of the aorta and its major branches that has a predilection to affect the extracranial branches of the carotid artery [5,6]. It is seen more frequently in women at a ratio of 2:1, and is the most common form of systemic vasculitis, with an incidence of 18.8 cases per 100,000 person-years in Olmstead County, Minnesota [7].

The predilection for GCA to occur in older patients has been considered by many to be a defining parameter in its diagnosis. Takayasu's arteritis, another form of large vessel vasculitis, predominantly affects women of childbearing age. However, the shared presence of granulomatous aortitis has raised the question as to whether these represent a similar underlying disease that can have a differing clinical spectrum.

Patients with GCA will typically present with headache, jaw or tongue claudication, scalp tenderness, constitutional features, or fever [8]. The most dreaded complication of GCA is vision loss caused by optic nerve ischemia from arteritis involving vessels of the ocular circulation [9,10]. Limb claudication reflecting involvement of the primary branches of the aorta occurs in 15% of cases [11]. Findings on physical examination in GCA include nodularity, tenderness, or absent pulsations of the temporal arteries or other involved vessels.

An elevated erythrocyte sedimentation rate (ESR) occurs in greater than 80% of patients, and when seen together with compatible clinical features, suggests the diagnosis of GCA. Temporal artery biopsy is confirmatory in 50% to 80% of cases with the demonstration of a panmural mononuclear cell infiltration that can be granulomatous with histiocytes and giant cells. To increase yield, the length of biopsy specimen should be at least 3 to 5 cm and sampled at multiple levels. In patients strongly suspected of having GCA, treatment should be instituted immediately to protect vision, while a prompt temporal artery biopsy is being arranged [12].

Glucocorticoids prevent visual complications in GCA and bring about a rapid improvement in clinical symptoms [9,13-15]. The optimal initial dosage has remained a point of differing opinion, but most investigators support that prednisone be initiated at a dose of 40 to 60 mg/d. In patients who present with acute visual loss, methylprednisolone 1 g/d for 3 days can be considered with the goal being to protect the remaining vision [16]. Symptomatic improvement usually occurs within the first 1 to 2 weeks after the initiation of prednisone accompanied by a reduction in ESR over the first month. Although there is no standardized prednisone tapering method,

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after 2 to 4 weeks when symptomatic improvement has occurred, prednisone can be reduced by 5-mg increments every 1 to 2 weeks until 20 mg is reached, at which time the decrements are made at 2- to 4-week intervals. After reaching a dosage of prednisone 10 mg/d, then the dosage would be reduced by 1-mg increments each month. Most patients require glucocorticoids for at least 2 years, with many receiving more than 4 years of treatment [17-22]. The ability of methotrexate (MTX) to decrease the occurrence of relapse and lessen glucocorticoid treatment was examined in 2 randomized studies that reaching different conclusions [23,24]. To date, no cytotoxic or biologic agent has been reproducibly found to effectively reduce the use of prednisone and lower its risk of side effects, although novel therapeutic approaches remain under active investigation. Current evidence supports that low-dose aspirin plays a beneficial role in reducing cranial ischemic complications in GCA and should be considered in all patients who do not have contraindications [25].

The clinical course of patients with GCA is assessed on the basis of symptoms and signs. ESR can be a useful parameter to follow but may remain elevated in some patients and is not consistently reliable in assessing disease activity or guiding therapy. Approximately 26% to 90% of patients experience one or more relapses requiring an increase or reinstitution of prednisone [17,18,20–22,24].

Acute mortality from GCA is uncommon, although thoracic aortic aneurysms may occur as a late complication of disease and can be associated with rupture and death [26,27]. Morbidity may occur as a result of ocular or large vessel disease or from glucocorticoid-related toxicities.

Polymyalgia rheumatica (PMR) is characterized by aching and morning stiffness along the proximal muscles of the shoulder and hip girdle [28,29]. PMR can occur in 40-50% of patients with GCA or as an isolated entity in which 10% to 15% of patients may later go onto have GCA. This clinical association together with evidence from the laboratory has supported that PMR and GCA represent clinical subsets of a single disease process [30,31]. The diagnosis of isolated PMR is based on consistent symptoms together with acute phase parameters that include an increased ESR and anemia. Further support for the diagnosis of PMR is provided by a rapid symptomatic response to prednisone 10 to 20 mg/d. Similar to GCA, the prednisone dosage is tapered slowly based on symptoms and acute phase parameters and may require dosage increases for clinical relapses [32]. The use of MTX in PMR has been examined, and use of this agent must be weighed against its risks [33,34].

Medium vessel vasculitis

Polyarteritis nodosa

As understanding of the vasculitides has grown, the classification of PAN has undergone a number of changes. In the nomenclature system published

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in 1994 from the Chapel Hill Consensus Conference, PAN was defined by the presence necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules [3,35]. Using this definition, PAN is believed to be very uncommon, but it remains an important multisystem illness that can present acutely in older patients [36].

The most common clinical manifestations of PAN include hypertension, fever, musculoskeletal symptoms, and vasculitis involving the nerve, gastrointestinal tract, heart, and nonglomerular renal vessels. Laboratory findings reflect an acute inflammatory process with anemia, leukocytosis, thrombocytosis, and an increased ESR. Antineutrophil cytoplasmic antibodies (ANCA) are uncommon in patients with PAN [37].

The diagnosis of PAN is made on the basis of biopsy or arteriography results. Biopsies of clinically involved areas such as the peripheral nerve or testicle reveal necrotizing inflammation involving the medium-sized or small arteries with abundant neutrophils, fibrinoid changes, and disruption of the internal elastic lamina. Arteriography is most often performed of the visceral and renal circulation, and shows microaneurysms, stenoses, or a beaded pattern with areas of arterial narrowing and dilation.

Patients with immediately life-threatening disease affecting the gastrointestinal system, heart, or central nervous system (CNS) should be treated with daily cyclophosphamide (CYC) 2 mg/kg/d and glucocorticoids [38 40]. In patients in whom the disease manifestations do not pose an immediate threat to life or major organ function, glucocorticoids alone can be considered as initial therapy with CYC being added in patients who continue to have evidence of active disease or who are unable to taper prednisone [39,41]. Relapses occur in less than 10% of patients with PAN [39].

A PAN-like vasculitis can also be seen in patients infected with hepatitis B, hepatitis C or the human immunodeficiency virus (HIV) [42]. In these settings, antiviral therapy should be part of the treatment regimen with the goal being to contain viral replication and favor seroconversion. To initially gain control of the vasculitis, patients may require glucocorticoids, alone or combined with CYC depending on the disease severity. Some investigators also advocate the use of plasmapheresis [43–45]. Once clinical improvement is observed, immunosuppressive therapies should be withdrawn rapidly while antiviral treatment is continued because the virus will persist and replicate in the setting of immunosuppression.

The estimated 5-year survival rate of PAN with treatment is 80%, with mortality being influenced by disease severity [39].

Small vessel vasculitic diseases

Vasculitis involving the small vessels clinically manifests in a variety of ways that can include cutaneous vasculitis, alveolar hemorrhage, and

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glomerulonephritis. These features can be seen in a spectrum of diseases that may have differing clinical presentations and severity.

Small vessel vasculitis is a prominent feature of 3 important forms of primary systemic vasculitis: Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS). Although these disease entities possess unique features, because they share similar involvement of the small vessels, glomerular histology, and the frequent association with ANCA, these diseases have been grouped together by some investigators for the purposes of therapeutic and epidemiologic studies.

The age of onset for the small vessel vasculitides has been an interesting area of epidemiologic investigation. Although some WG series have found a median age of diagnosis in the 1940's [46,47], 2 studies from Europe found a much older age of disease presentation. In a study conducted in Sweden, Tidman and colleagues [48] found a frequency peak for ANCA-associated vasculitides in men ages 55 to 64 years. Watts and associates [49] in the United Kingdom found the occurrence of primary systemic vasculitis to increase with age with a peak in the 65- to 74-year-old age group. These experiences underscore that the small vessel vasculitic diseases should remain a diagnostic consideration in all patients, regardless of age.

Wegener's granulomatosis

Wegener's granulomatosis is characterized by a granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting the small to medium-sized vessels in which glomerulonephritis is common [46,47]. More than 90% of patients first seek medical attention for symptoms related to the upper or lower airways. Nasal and sinus mucosal inflammation may result in nasal crusting and epistaxis with the potential for nasal septum perforation or collapse of the nasal bridge. A diverse range of pulmonary radiographic abnormalities can be seen including single or multiple nodules or infiltrates, cavities, and ground glass infiltrates. Glomerulonephritis can be rapidly progressive and asymptomatic and is detected by the presence of an active urine sediment with microscopic hematuria and red blood cell casts. Although the sinuses, lungs, and kidneys are the most frequently affected locations, WG is a multisystem disease that can involve the eyes, skin, nerve, and heart with potentially serious consequences.

Wegener's granulomatosis is highly ANCA associated [50,51]. Two types of ANCA have been identified in patients with a primary systemic small vessel vasculitis: ANCA that target the neutrophil serine protease, proteinase 3 (PR3) that causes a cytoplasmic immunofluorescence pattern (cANCA) on ethanol-fixed neutrophils [52] and ANCA directed against the neutrophil enzyme myeloperoxidase (MPO) that generate a perinuclear immunofluorescence pattern (pANCA) [53]. Approximately 75% to 90% of patients with active WG have PR3-ANCA, whereas 5% to 20% may have MPO-ANCA. With the exception of patients who present with sinus, lung, and renal disease, the predictive value of ANCA is usually insufficient to render

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a diagnosis of WG. ANCA levels are not a static and will vary during the course of a patient's illness. Although cohort studies observed that patients with active disease had higher levels of ANCA compared with those who were in remission [50,54], changes in sequential ANCA measurement in an individual patient have not been found to be uniformly reliable for assessing disease activity or predicting relapse and should not be used to guide treatment [55,56]. The role of ANCA in disease pathogenesis remains an active area of investigation [57,58].

The diagnosis of WG is usually based on the presence of characteristic histologic findings in a clinically compatible setting. Nonrenal tissues show granulomatous inflammation; necrosis, often with aggregates of neutrophils; and necrotizing or granulomatous vasculitis. Surgically obtained biopsies of abnormal pulmonary parenchyma yield diagnostic changes in 91% of cases [59]. Biopsies of the upper airways are less invasive but find diagnostic features only 21% of the time [60]. The characteristic renal histology is that of a focal, segmental, necrotizing, crescentic glomerulonephritis with few to no immune complexes [61].

The outcome for patients with WG dramatically improved when Fauci and Wolff introduced combined therapy with CYC 2 mg/kg/d and prednisone 1 mg/kg/d [62,63]. This regimen has reproducibly been found to induce remission in 75% to 100% of patients with active WG [46,64,65]. After the first 4 weeks of treatment, if there is evidence of improvement, the prednisone is tapered and discontinued by 6 to 12 months. In the setting of fulminant disease, methylprednisolone 1 g/d may be given in combination with CYC 3 to 4 mg/kg/d for 3 days after which time the dosage is reduced to 2 mg/kg/d [63]. CYC is associated with substantial toxicity including bone marrow suppression, bladder injury, infertility, myeloproliferative disease, and transitional cell carcinoma of the bladder [66]. To reduce the risk of toxicity, staged therapeutic approaches are now used in which the duration of CYC exposure is limited to the 3- to 6-month period required to induce remission. After that time, CYC is stopped and switched to azathioprine (AZA) 2 mg/kg/d [65] or MTX 20 to 25 mg/wk [64,67] to maintain remission. Mycophenolate mofetil 1000 mg twice a day has also been examined in open-label studies and may be considered for remission maintenance after CYC induction, particularly in patients who cannot take or who have relapsed through AZA or MTX [68,69]. In patients who have active but non life-threatening disease who do not have renal or hepatic contraindications, MTX 20 to 25 mg/wk together with prednisone, can be used to induce and maintain remission [70,71]. The optimal duration of maintenance therapy remains unclear [72]. After initial diagnosis, maintenance therapy is often given for 2 years, after which time if the patient remains in remission, consideration may be given for tapering and discontinuation. For patients who have had repeated relapses or significant irreversible organ damage from past disease, continuing maintenance therapy for a longer duration may be warranted in the absence of medication side effects.

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The use of biologic therapies in WG has been increasingly investigated. A recent randomized, double-blind, placebo-controlled trial found that etanercept was not effective in the maintenance of remission in patients with WG [73]. This study also suggested that the combination of tumor necrosis factor (TNF) inhibition and CYC may heighten the risk of cancer beyond that observed with CYC alone [74]. Experience with infliximab from an open-label study found that severe infections occurred in 21% of patients, and that despite continued infliximab, 20% of initial responders experienced disease relapse [75]. At this time, these collective data do not support the use of any TNF modulatory agent in WG. Favorable results with the use of rituximab, an anti-CD20 B-cell depleting monoclonal antibody, have prompted further study of this agent in WG through an ongoing randomized trial [76,77]. Until further experience has been gained, rituximab should not be used in place of standard treatments that have an established efficacy.

Despite the ability to successfully induce remission, relapse occurs in at least 50% of patients with WG. The ability of trimethoprim/sulfamethoxazole (T/S) to reduce relapse was examined in a randomized trial. Although an overall higher rate of relapse at 24 months was observed in patients who received placebo compared with T/S, T/S did not lessen relapses involving organ systems outside of the upper airways when examined by organ system [78]. As discussed later in this review, one of the most important roles for T/S in WG is in the prevention of *Pneumocystis jiroveci* pneumonia. In patients receiving MTX, T/S can be administered safely at prophylactic doses but should not be given twice daily because bone marrow suppression can occur [79].

Before the introduction of treatment, WG was uniformly fatal. Effective therapy has brought the potential for long-term survival, although substantial morbidity can still result from both the disease and its treatment.

Microscopic polyangiitis

Microscopic polyangiitis is characterized by necrotizing vasculitis with few or no immune deposits affecting small vessels. It was nosologically separated from PAN in conjunction with the Chapel Hill consensus definitions, and limited data remain on this entity as an independent process [3]. MPA has many similarities to WG but is currently said to be differentiated by the absence of granulomatous inflammation.

The presentation of MPA can be acute and severe, with features including glomerulonephritis, pulmonary hemorrhage, mononeuritis multiplex, and fever [80,81]. MPA is diagnosed by histologic demonstration of necrotizing vasculitis of the small vessels or small to medium-sized arteries in which granulomatous inflammation is absent. Biopsies of lung tissue typically find capillaritis, hemorrhage into the alveolar space, and the absence of immunofluorescence as would be seen in antiglomerular basement membrane antibody disease (Goodpasture's syndrome). The renal histology is similar to that observed in WG in being a focal segmental necrotizing glomerulonephritis with few to no immune complexes. MPA is also highly

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ANCA associated with 50% to 80% having MPO-ANCA, whereas 10% to 50% may be PR3-ANCA positive.

Patients with MPA should be treated initially with CYC 2 mg/kg/d and prednisone 1 mg/kg/d with transition to a less toxic maintenance agent after remission as discussed for WG [65,81,82]. Relapses occur in at least 34% of patients with MPA with the estimated 5-year survival rate being 74% [80].

Churg-Strauss syndrome

Churg-Strauss syndrome is a rare disease characterized by asthma, peripheral and tissue eosinophilia, and necrotizing vasculitis affecting the small to medium-sized vessels [83–86]. CSS has been thought of as having three phases: a prodromal phase, with allergic rhinitis and asthma, a phase characterized by peripheral eosinophilia and eosinophilic tissue infiltrates, and ultimately vasculitic disease that can involve the nerve, lung, heart, gastrointestinal tract, and kidney. These phases may not be clinically identifiable in all patients, and they often do not occur in sequence.

Histologic features of CSS include eosinophilic tissue infiltrates, extravascular "allergic" granuloma, and small vessel necrotizing vasculitis [83]. The constellation of clinical manifestations in CSS is of great importance in the diagnosis, because evidence of vasculitis can be difficult to establish. ANCA are less commonly seen in CSS with 3% to 35% having PR3-ANCA and 2% to 50% having MPO-ANCA.

Prednisone 1 mg/kg/d is effective for many manifestations of CSS. Relapses of vasculitic disease occur in at least 26% of CSS patients and asthma often persists after remission of the vasculitis, limiting the ability for prednisone dosages to be completely tapered [84]. It is unclear whether an association exists between leukotriene antagonists and CSS, and use of these agents should be avoided [87]. Combined therapy with glucocorticoids and CYC 2 mg/kg/d in CSS is reserved for patients with life-threatening vasculitis.

The outcome of patients with CSS is influenced by the presence of severe disease involving sites such as the heart, gastrointestinal tract, CNS, and kidney. Cardiac involvement is the main cause of patient mortality and is a poor prognostic sign.

Isolated cutaneous vasculitis

Cutaneous vasculitis is the most commonly encountered vasculitic manifestation. Cutaneous vasculitis typically manifests as palpable purpura but may present as necrotic papules or ulcerative lesions [88,89]. Cutaneous vasculitis is histologically characterized by the presence of small vessel inflammation within the dermis, often with leukocytoclasis.

In more than 70% of cases, cutaneous vasculitis occurs secondary to an underlying disease or exposure or as a heralding feature of a primary vasculitic disease [88–90]. An isolated idiopathic cutaneous vasculitis should only be diagnosed after other causes have been ruled out. Biopsy of a skin lesion

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can confirm the presence of vasculitis and provide clues to the underlying process through cultures and immunofluorescence studies.

The course of idiopathic cutaneous vasculitis can range from a single episode to multiple protracted recurrences, and progression to a systemic vasculitis occurs infrequently. There are no uniformly effective treatments for idiopathic cutaneous vasculitis, and the least toxic treatment that provides benefit should be used. Glucocorticoids, nonsteroidal anti-inflammatory agents, antihistamines, dapsone, and colchicine have been used. Because idiopathic cutaneous vasculitis is limited to the skin, the risks of cytotoxic agents must be weighed against the uncertain benefits and should be reserved for very select cases in which patients have severe disease that is unresponsive to other measures or when glucocorticoid dosages cannot be tapered.

Henoch-Schönlein purpura

Henoch-Schönlein purpura (HSP) is a small vessel vasculitis characterized by the presence of IgA-dominant immune deposits [91]. Although HSP predominantly affects children, with 75% of cases occurring before 8 years of age, adults can rarely be affected.

The clinical manifestations of HSP include palpable purpura, arthritis, glomerulonephritis, and gastrointestinal involvement. Less is known about HSP in adults, although several findings suggest that a more severe clinical syndrome may occur, particularly with regard to glomerulonephritis [92–94].

The diagnosis of HSP is established by the characteristic pattern of clinical manifestations. Skin biopsy reveals leukocytoclastic vasculitis with IgA deposition in blood vessel walls.

Henoch-Schönlein purpura is a self-limited condition that rarely requires treatment. Glucocorticoids are of no proven benefit in skin or renal disease and do not appear to lessen the likelihood of relapse. In patients with glomerulonephritis who have a rising creatinine level, treatment with CYC and prednisone may be considered. Outcome data largely come from pediatric series in which recurrence occurs in up to 40% of cases. Disease-related mortality occurs in only 1% to 3% of patients.

Secondary vasculitides

Vasculitis occurring secondary to an underlying disease or exposure represents a significant proportion of the vasculitis that is encountered in clinical practice.

Secondary vasculitis most commonly occurs in association with medications, malignancies, infection, or connective tissue diseases [88–90]. Particularly in geriatric patients, the potential for a neoplastic disease or a medication reaction must be examined carefully in any patient who presents with a new cutaneous vasculitis.

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Secondary vasculitis often is isolated to the skin, although systemic vasculitis can occur in conjunction with a connective tissue disease, cryoglobulinemic vasculitis, or, rarely, in conjunction with a medication. An increasing number of medications have been reported to cause vasculitis in association with a positive ANCA. The agents reported to cause ANCA-associated drug-induced vasculitis include propylthiouracil, hydralazine, penicillamine, minocycline, sulfasalzine, and others [95]. The clinical manifestations in affected patients range from cutaneous disease to glomerulonephritis and pulmonary hemorrhage. In suspected cases, the drug should be withdrawn, and immunosuppressive treatment initiated based on the degree of severity of the vasculitis.

Cryoglobulinemic vasculitis

Cryoglobulins are cold-precipitable monoclonal or polyclonal immunoglobulins. Cryoglobulinemia can be associated with a small vessel vasculitis characterized by palpable purpura, arthritis, weakness, neuropathy, and a membranoproliferative glomerulonephritis [96–98]. Cryoglobulinemic vasculitis most commonly occurs in the setting of chronic hepatitis C viral infection (HCV), but can also be seen with plasma cell or lymphoid neoplasms, infection, inflammatory diseases, or rarely as an idiopathic process [96].

Laboratory features of cryoglobulinemic vasculitis include circulating cryoglobulins, a positive rheumatoid factor, hypocomplementemia, and an elevated ESR. Biopsies of the skin and kidney typically are not required for diagnosis but can be useful in showing deposition of immunoglobulin or complement by immunofluorescence.

Management of cryoglobulinemic vasculitis is directed toward treatment of the underling disease. Antiviral therapy provides the best opportunity for improvement of cryoglobulinemic vasculitis occurring in association with HCV, but long-term resolution is limited to patients who have a sustained virologic response [98,99]. Immunosuppressive therapies and plasmapheresis have been used with brief improvement but are associated with toxicities that preclude them from being effective long-term treatment options. Recent studies have began to explore the use of rituximab in HCV-associated cryoglobulinemic vasculitis, but further investigation is needed to understand its safety and efficacy in this disease [100,101].

Cryoglobulinemic vasculitis represents a chronic process in which mortality is usually related to the underlying disease rather than the vasculitis.

Management considerations in the geriatric vasculitis patient

Impact of comorbid diseases

Geriatric patients frequently will have other medical illnesses that can influence the signs and symptoms of a vasculitic disease. This is best exemplified by pulmonary vasculitis in which the appearance of radiographic

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nodules or infiltrates in an older patient may appropriately raise concern for a neoplasm or infection. Concomitant factors such as tobacco use, chronic obstructive pulmonary disease, or other lung disorders may also influence clinical and radiographic presentations.

The presence of comorbid diseases can also affect vasculitis care after diagnosis. Worsening signs or symptoms of an underlying disease could have a similar appearance to vasculitis. In a patient with atherosclerotic coronary artery disease and a systemic vasculitis, new dyspnea and pulmonary infiltrates could be related to a variety of causes that include congestive heart failure, active vasculitis, a medication reaction, or infection.

Increased risk of medication toxicities

Treatment-related toxicities influence outcome in patients with vasculitis and can present unique challenges in older individuals. Awareness, monitoring, and prevention of medication side effects play an important role in minimizing risk in geriatric patients.

Infection

Infection is a prominent cause of morbidity and mortality in vasculitis patients and can develop in association with any type of immunosuppressive therapy. In one series of 43 prednisone-treated GCA patients, sepsis and other infectious complications were responsible for 6 of the 19 (32%) observed fatalities seen during the study period [102]. Infection risks are compounded when a cytotoxic agent is used in combination with glucocorticoids. Infections have been reported to occur in 10% to 70% of WG patients [46,64,65,103], and in a long-term survival study of WG patients from the American College of Rheumatology Classification Criteria cohort, Matteson and colleagues [104] found infection to be the number one cause of death responsible for 29% of patient fatalities.

Pneumocystis jiroveci pneumonia is a serious opportunistic infection that has been found to occur in approximately 10% of WG patients receiving prednisone in combination with a cytotoxic agent [71,105]. Although large-scale studies in other vasculitic diseases are not available, the presence of published case reports suggests that vasculitis patients who receive similar treatment regimens are also at risk of Pneumocystis. Because of this association, it is recommended that all patients with a vasculitic disease who are receiving combined therapy with glucocorticoids and a cytotoxic agent be given Pneumocystis prophylaxis. Based on the experience in HIV and leukemia, trimethoprim 160 mg/sulfamethoxazole 800 mg 3 times weekly or trimethoprim 80 mg/sulfamethoxazole 400 mg daily is recommended [106]. For patients with a severe sulfa allergy, atovaquone 1500 mg daily or inhaled pentamidine 300 mg every 3 to 4 weeks may be considered.

Influenza is a potentially life-threatening infection in all geriatric patients. There has been no clear evidence to suggest that influenza immunization has

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a deleterious impact on vasculitis or its treatment, and it is therefore recommended that all geriatric vasculitis patients continue to receive annual influenza vaccinations. Vasculitis patients should only receive inactivated influenza immunizations because live vaccinations are contraindicated in immunosuppressed hosts.

Glucocorticoids

Glucocorticoids comprise an essential therapeutic component for almost all forms of primary systemic vasculitis that affect adults. In GCA, 35% to 65% of treated patients have been found to experience glucocorticoid-related toxicity [102,107]. Glucocorticoids possess a broad range of potential side effects, many of which can occur at an increased frequency or have greater potential for clinical impact in geriatric patients.

Osteoporosis

Glucocorticoids have been well established to reduce bone density and by so doing, place geriatric patients at greater risk of fractures [102,107,108]. Although postmenopausal women are subject to the greatest risk of bone loss, glucocorticoid-induced osteoporosis can also develop in men. Glucocorticoid-treated patients should undergo a baseline dual-energy x-ray absorptiometry early in treatment with regular monitoring thereafter. Preventive measures to reduce the risk of bone loss and fractures should be initiated in all glucocorticoid-treated patients and include the use of exercise, calcium, and bisphosphonates in eligible patients and evaluation of the home for fall risks.

Cataracts

Cataracts can occur in a high percentage of glucocorticoid-treated patients. In one series of patients with WG, 21% had glucocorticoid-related cataracts [46]. For patients who may already have established cataract formation, progression may accelerate to the point of significantly impairing vision. Ophthalmologic assessment at baseline and at regular intervals can be useful in monitoring for cataract development.

Diabetes mellitus

Glucose intolerance can develop in glucocorticoid-treated patients. In one study, patients with PMR had greater than 2 times the risk of diabetes mellitus compared with age- and sex-matched individuals from the same community [107]. Counseling regarding diet and monitoring of the serum glucose are important in the care of geriatric vasculitis patients who receive glucocorticoid treatment.

Hypertension

Hypertension is a critical cardiovascular risk factor for complications involving the heart, brain, and kidneys. The presence of renal vascular disease

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affecting the large, medium, or small vessels and glucocorticoid treatment increases the potential for hypertension in vasculitis patients. Management of hypertension in geriatric patients must take into account the presence of comorbid diseases, medication interactions, and the course of the vasculitic disease and its management.

Myopathy

Myopathy can result from glucocorticoid therapy and most commonly presents as weakness in the proximal muscles of the shoulder and hip girdle limiting the ability to rise from a chair or go up stairs. Glucocorticoid myopathy can be differentiated from muscle weakness from other causes by location and the presence of normal muscle enzymes. Muscle weakness will characteristically improve as the glucocorticoid dosage is lowered and may be helped by physical therapy. If myopathy is present, caution for falls should be raised, and a careful assessment of the home should be undertaken to reduce the risk for potential injuries.

Cytotoxic therapies

For many vasculitic diseases, optimal treatment includes the use of cytotoxic agents such as CYC, MTX, or AZA. Although these therapies each have individual side effects, there are potential concerns that apply to many of these agents when prescribed in geriatric patients.

Cytopenias

Cyclophosphamide, MTX, AZA and many other cytotoxic agents are suppressive to the bone marrow. Geriatric patients receiving cytotoxic treatment may be particularly prone to the development of cytopenias, which can place them at risk of infection, bleeding, or anemia. In addition to caution regarding dosing, the most important measure that can be taken to minimize the occurrence of cytopenias is to perform frequent monitoring of the complete blood counts. Patients receiving CYC should have their blood counts monitored every 1 to 2 weeks. Blood counts should be performed in patients receiving MTX and AZA every 1 to 2 weeks during dosage adjustment and every 4 weeks thereafter.

Impact of renal function

Cyclophosphamide and MTX are both eliminated renally making underlying kidney function an important parameter in dosing and protection. An association between age and decreasing glomerular filtration rate has been suggested by several studies. Accurate assessment of renal function may be confounded in older patients by the presence of comorbid diseases, medications, and low muscle mass. Depending on the clinical setting, reduction of CYC dosage may be indicated in patients with renal insufficiency. MTX is contraindicated in patients with a creatinine clearance less than 35 mL/min

or serum creatinine level of greater than 2.0 mg/dL, because ineffective elimination can lead to severe toxicity. AZA is not contraindicated in renal insufficiency and can be considered in the treatment of vasculitic diseases where data have shown its benefit.

Medication interactions

Medications that are being used to treat another underlying disease may have important interactions with agents that are used to treat vasculitis. Allopurinol inhibits the metabolism of AZA leading to increased AZA levels when taken together [109,110]. For patients who must remain on allopurinol for the treatment of gout, the dosage of AZA should be reduced by one third to one quarter of the usual dosage to avoid toxicity.

As noted in the WG section, weekly MTX and T/S given twice daily represents another important interaction that is associated with bone marrow toxicity [79].

Summary

The vasculitic diseases represent a diverse range of clinical entities that are linked by the presence of blood vessel inflammation. For many forms of vasculitis, older patients comprise a significant proportion of the affected population. Recognition of the forms of vasculitis that may affect geriatric patients and an appreciation of how the disease and its treatment may uniquely affect this age group can play a meaningful role in improving patient outcome and quality of life.

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