Perinuclear antineutrophil cytoplasmic antibody–associated vasculitis in an elderly woman

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EDITOR'S KEY POINTS

- A multisystem disease process not caused by infection or malignancy should raise concern about small-vessel vasculitis. Palpable purpura (raised and nonblanching) in the lower extremities is the most common and suggestive skin manifestation, and much less specific constitutional symptoms, such as fever, fatigue, arthritis, and renal and pulmonary involvement, are also common.
- Although not present in every patient, the presence of perinuclear antineutrophil cytoplasmic antibody (ANCA) or cytoplasmic ANCA can help distinguish among ANCA-associated small-vessel vasculitis subtypes (ie, eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, and microscopic polyangiitis).
- For patients with organ-threatening disease, treatment with glucocorticoids combined with cyclophosphamide or rituximab is recommended for inducing remission. Once remission is achieved after 3 to 6 months of induction therapy, maintenance therapy must be given for a minimum of 18 to 24 months, most often with azathioprine or methotrexate; the glucocorticoid dosage is tapered during this time.

POINTS DE REPÈRE DU RÉDACTEUR

- Un processus pathologique multisystémique qui n'est pas causé par une infection ou un cancer devrait soulever des préoccupations entourant la possibilité d'une vascularite des vaisseaux de petit calibre. Un purpura palpable (en relief et ne disparaissant pas à la pression) aux extrémités inférieures représente la manifestation dermatologique la plus courante et suggestive du problème. Des symptômes constitutionnels bien moins spécifiques, comme la fièvre, la fatigue, l'arthrite et une atteinte rénale et pulmonaire, sont aussi courants.
- Même si elle n'est pas observée chez tous les patients, la présence d'anticorps cytoplasmiques périnucléaires antineutrophiles (ANCA) ou ANCA cytoplasmiques peut aider à faire une distinction entre les sous-types de vascularites des vaisseaux de petit calibre associés aux ANCA (p. ex. granulomatose éosinophile avec polyangéite, granulomatose avec polyangéite et polyangéite microscopique).
- Pour les patients dont la maladie menace un organe, un traitement aux glucocorticoïdes combiné avec du cyclophosphamide ou du rituximab est recommandé pour induire la rémission. Lorsqu'une rémission est atteinte après une thérapie d'induction de 3 à 6 mois, un traitement d'entretien doit être administré pendant au moins 18 à 24 mois, le plus souvent avec de l'azathioprine ou du méthotrexate; durant ce temps, le dosage des glucocorticoïdes doit être diminué progressivement.

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Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis encompasses 3 conditions: eosinophilic granulomatosis with polyangiitis (EGPA; formerly named *Churg-Strauss syndrome*), granulomatosis with polyangiitis (GPA; formerly named *Wegener granulomatosis*), and microscopic polyangiitis.[1] Diagnosing ANCA-associated small-vessel vasculitis is challenging for clinicians because of its infrequent presentation (incidence of 20 per 1 million) and variable clinical manifestations.[1,2] Antineutrophil cytoplasmic antibody–associated small-vessel vasculitis generally presents as a multisystem disease.[2] Here we describe a case of ANCA-associated small-vessel vasculitis that underlines why it is important for family physicians to be familiar with this condition and to have an appropriately high index of suspicion to prevent life-threatening end-organ damage.[3]

Case

An 87-year-old non-smoking woman presented to the emergency department after experiencing multiple nonspecific symptoms during the previous 2 months including fevers, weight loss, generalized arthralgia, headaches, chronic nonproductive cough, and progressive proximal leg weakness. Her past medical history was relevant for hypertension, type 2 diabetes, asthma, and bilateral lung nodules. She reported no sick contacts or recent travel outside of Canada.

Physical examination findings were unremarkable except for a fever of 38.3°C and bilateral proximal lower extremity weakness. A complete blood count revealed microcytic anemia (hemoglobin level of 93 g/L and a mean corpuscular volume of 77 fL), neutrophilia (neutrophil count of 18.6×10^9/L), a normal eosinophil count (0.2×10^9/L), an elevated erythrocyte sedimentation

rate (51 mm/h), an elevated C-reactive protein level (1828.61 nmol/L), and hypoalbuminemia (albumin level of 21 g/L). Renal function test results suggested acute kidney injury, with a creatinine level of 317 µmol/L (compared with her baseline level of 70 to 80 µmol/L). Urine test results revealed microscopic hematuria (30 to 50 red blood cells per high-power field) with casts. Her test results were positive for perinuclear ANCA (p-ANCA) on indirect immunofluorescence and myeloperoxidase antibodies (5.7 IU/L) on enzyme-linked immunosorbent assay (ELISA), and were negative for cytoplasmic ANCA (c-ANCA), antinuclear antibodies, and anti–glomerular basement membrane antibodies. Her creatine kinase and angiotensin-converting enzyme levels were normal. Infection screening and tuberculin skin test results were negative. Findings of a computed tomography scan of her chest revealed several ill-defined plain nodules throughout both lungs, with no adenopathy.

The patient was admitted to hospital and diagnosed with p-ANCA–associated GPA. She was given pulse therapy with intravenous methylprednisolone (500 mg/d) for 3 days, with tapering to oral prednisone (40 mg/d). Findings of a kidney biopsy done just before starting treatment revealed pauci-immune necrotizing glomerulonephritis and focal segmental necrotizing glomerulosclerosis. The patient's renal function, lung nodules, and muscle weakness improved with glucocorticoid therapy.

Discussion

Vasculitis is inflammation of blood vessel walls and it can result in tissue ischemia or infarction.[2] Vasculitis is classified based on the size of the blood vessels involved and can be primary (no known cause) or secondary (triggered by an infection or caused by an inflammatory disease or malignancy).[1] Small-vessel vasculitis affects vessels smaller than arteries (ie, arterioles, capillaries, and venules).[1]

Family physicians should be aware of the potential clinical manifestations of small-vessel vasculitis, which are shown in **Table 1**.[1-3] A multisystem disease process not caused by infection or malignancy should raise concern about small-vessel vasculitis.[3] Palpable purpura (raised and nonblanching) in the lower extremities is the most common and suggestive skin manifestation.[3] Much less specific constitutional symptoms, such as fever, fatigue, arthritis, and renal and pulmonary involvement, are also common manifestations of small-vessel vasculitis, sometimes occurring in isolation for several weeks at disease onset.[2,3] It is important to differentiate small-vessel vasculitis from other conditions that can cause multisystem symptoms. The differential diagnosis includes anti–glomerular basement membrane antibody disease, antiphospholipid syndrome, cocaine use, hypersensitivity reactions, multiple myeloma, paraneoplastic syndromes, and secondary causes of vasculitis (ie, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, cancer, and hepatitis B and C infections).[3] Typical laboratory findings for vasculitis are anemia, leukocytosis, elevated inflammatory markers, and renal findings with abnormal urinalysis results.[3]

To help determine the type of small-vessel vasculitis, testing for ANCA should be completed.[2,4] Antineutrophil cytoplasmic antibodies work against neutrophil antigens and show 2 important staining patterns: c-ANCA, mainly seen with antibodies to proteinase 3 on ELISA, and p-ANCA, mainly seen with antibodies to myeloperoxidase on ELISA.[2] Although not present in every patient, the presence of p-ANCA or c-ANCA can help further distinguish among ANCA-associated small-vessel vasculitis subtypes.[2] As previously discussed, ANCA-associated small-vessel vasculitis can be subdivided into EGPA, GPA, and microscopic polyangiitis.[1] Test results for c-ANCA are positive in 75% to 90% of GPA cases, while the presence of p-ANCA is more characteristic of microscopic polyangiitis and EGPA.[2,3] **Table 2** shows clinical features of ANCA-associated small-vessel vasculitis.[1-3]

Treatment involves 2 phases: induction and maintenance.[3] For patients with organ-threatening disease, treatment with glucocorticoids combined with cyclophosphamide or rituximab is recommended for inducing remission.[3,4] The patient in the presented case did not receive cyclophosphamide or rituximab because her condition was clinically much improved by the time she presented to the vasculitis clinic. However, glucocorticoids

Table 1. Most common clinical manifestations of small-vessel vasculitis

SYSTEM	CLINICAL MANIFESTATIONS
Constitutional	Fatigue, fever (>38°C), weight loss (≥2 kg), night sweats
Ear, nose, and throat	Bloody nasal discharge, subglottic stenosis, ulcers
Gastrointestinal tract	Abdominal pain, bloody diarrhea
Kidneys	Hypertension, proteinuria, microscopic hematuria, renal insufficiency, necrotizing glomerulonephritis, renal failure
Musculoskeletal system	Arthralgia, myalgia
Nervous system	Neuropathy (mononeuropathy multiplex), headache
Respiratory tract	Dyspnea, cough, asthma (EGPA), hemoptysis, alveolar hemorrhage, lung infiltrates, lung nodules, pleural effusions
Skin	Palpable purpura, urticarial rash

EGPA—eosinophilic granulomatosis with polyangiitis.
Adapted from Jennette et al,[1] Jennette and Falk,[2] and Sharma et al.[3]

Table 2. Most typical clinical features of ANCA-associated small-vessel vasculitis

SMALL-VESSEL VASCULITIS	MAIN ORGANS INVOLVED	AGE OF ONSET, Y	MARKERS	OTHER CHARACTERISTIC FEATURES
Eosinophilic granulomatosis with polyangiitis	Lungs, heart	50-60	p-ANCA	Asthma and peripheral blood eosinophilia
Granulomatosis with polyangiitis	Upper and lower respiratory tracts, kidneys	40-50	c-ANCA	Pulmonary nodules with cavitation, chronic eroding rhinosinusitis, pauci-immune glomerulonephritis
Microscopic polyangiitis	Lungs, skin, kidneys	50-60	p-ANCA	Pauci-immune glomerulonephritis, pulmonary capillaritis, purpura

ANCA—antineutrophil cytoplasmic antibody, c-ANCA—cytoplasmic ANCA, p-ANCA—perinuclear ANCA.
Adapted from Jennette et al,[1] Jennette and Falk,[2] and Sharma et al.[3]

alone are generally not sufficient and cyclophosphamide or rituximab are needed to induce remission. Glucocorticoids are given orally (1 mg/kg/d, up to 60 mg/d), possibly preceded by pulsed intravenous doses of methylprednisolone (7.5 to 15 mg/kg/d) for the first 3 days, with oral cyclophosphamide (1 to 2 mg/kg/d, up to 200 mg/d, adjusted for renal function and patient age) or intravenous pulsed cyclophosphamide (7.5 to 15 mg/kg per pulse, on days 1, 15, and 29, and then every 3 weeks).[4,5] Rituximab can be used if these standard treatments fail or in case of contraindications to cyclophosphamide use.[4,6] For patients with life-threatening disease (eg, pulmonary hemorrhage, severe renal failure), additional treatment with plasma exchange can be considered.[3,4,7] Once remission is achieved after 3 to 6 months of induction therapy, maintenance therapy must be given for a minimum of 18 to 24 months, most often with azathioprine or methotrexate (repeat low-dose rituximab infusions might become another maintenance option in the future); the glucocorticoid dosage is tapered during this time.[3,4] As all these treatments are immunosuppressive, family physicians should closely monitor patients for potential complications, such as infections and hemorrhagic cystitis,[4] in collaboration with centres that specialize in vasculitis such as those listed at **www.canvasc.ca**.

Conclusion

As family physicians are frequently the first point of contact for patients with ANCA-associated small-vessel vasculitis, it is important to be aware of the common clinical manifestations of this condition, which can lead to life-threatening organ failure if not diagnosed and treated promptly. In caring for these complex patients, family physicians often collaborate with various other specialists.

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Competing interests
None declared

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