Practice Gaps in Cutaneous (Small-Vessel) Vasculitis

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American Academy of Dermatology, Summer Meeting, Boston, MA
Forum F004: Practice Gaps in Adult and Pediatric Dermatology: Illustrative Cases
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Disclosure

• I have no conflicts of interest
Overview

• Discuss 4 clinical insights of cutaneous small-vessel vasculitis based on Mayo Clinic research that addresses practice gaps

• (IF TIME) Briefly discuss my approach to the evaluation and management of cutaneous small-vessel vasculitis
  • In order to carry the practice gaps discussed into “real-world clinical practice”

• Take home messages
PRACTICE GAP #1

• *Can solid-organ malignancy be a cause of cutaneous vasculitis?*
• 37 year-old man with IgA vasculitis of the skin and kidneys

• Treated with low-dose dapsone (50 mg daily) and tapering course of prednisone (60 mg daily) over 1 month

• Two weeks after presentation was admitted to hospital and computed tomography (CT) scan was performed to evaluate abdominal pain

CT of the abdomen and pelvis with intravenous contrast. No comparison. There is a 1.6cm solid enhancing exophytic mass off the posterior lower pole of the right kidney that is suspicious for renal cell carcinoma. US would be helpful. Splenic granulomata. Benign-appearing abdominal calcification (series 2, image 39). Otherwise, negative.

**DIAGNOSIS:**
Kidney, right, partial nephrectomy: Grade 1 (of 4) renal cell carcinoma, clear cell type, forms a 1.1 x 1.1 x 1.0 cm mass located in the right lower lobe pole. Coagulative tumor necrosis is absent. Sarcomatoid differentiation is absent. The surgical margins are negative for tumor (locally by <0.1 cm).

- Final diagnosis: IgA vasculitis associated with renal cell carcinoma
- Skin lesions completely resolved with no new lesions in the subsequent months after resection of malignancy
Cutaneous Vasculitis and Malignancy

- Associated in 2-5% of cases (Fiorentino JAAD 2003;48:311-40)

- Usually hematologic malignancy (Fain et al. Arthritis Rheum 2007;57(8):1473-80)

- Unclear relationship between cutaneous small-vessel vasculitis (CSVV) and solid organ malignancy
  - Various malignancies reported
  - Can signal malignancy recurrence (Fortin PR Curr Opin Rheumatol 1996:8(1):30-3)
ETIOLOGIES OF CUTANEOUS SMALL VESSEL VASCULITIS

Infection (15–20%)
Autoimmune connective tissue disease (15–20%)
Drug (10–15%)
Neoplasm (5%)
Idiopathic (45–55%)

Chung, Kea, Fiorentino: “Dermatology” 2008 (2nd ed), Chapter 25
CSVV and solid organ malignancy: 

*What is the Mayo experience?*
Cutaneous small-vessel vasculitis associated with solid organ malignancies: The Mayo Clinic experience, 1996 to 2009

Joshua O. Podjasek, MD, David A. Wetter, MD, Mark R. Pittelkow, MD, and David A. Wada, MD
Rochester, Minnesota

Background: Although rare, cutaneous small-vessel vasculitis (CSVV) secondary to solid organ malignancy has been documented.

Objective: We sought to better understand the frequency, clinical course, therapeutic response, and outcome of CSVV associated with solid organ malignancy.

Methods: We conducted a retrospective chart review of patients seen between 1996 and 2009 with diagnoses of biopsy-proven cutaneous leukocytoclastic vasculitis and solid organ malignancy separated by less than 12 months.

Results: Of 17 patients (mean age, 66.5 years), 10 patients (59%) were male. CSVV occurred before (3 patients; 18%), concurrent with (3 patients; 18%), and after (11 patients; 65%) diagnosis of solid organ malignancy. The most common solid organ malignancy was the lung (n = 4; 24%). Other associated cancers were breast (n = 3); prostate (n = 2); colon (n = 2); renal (n = 2); thyroid (n = 1); bladder (n = 1); gallbladder (n = 1); and peritoneal (n = 1). Three patients had cutaneous vasculitis in association with malignancy recurrence despite having no cutaneous vasculitis associated with their primary malignancy. Vasculitis remission with use of immunosuppressive agents alone occurred in 9 patients (53%). Eleven patients (65%) were alive at last follow-up (mean follow-up duration, 27 months).

Limitations: This was a retrospective study with a relatively small number of patients.

Conclusion: Solid organ malignancy should be considered as a possible cause of CSVV of unknown origin. In contrast to previous reports, our patients were more likely to respond to immunosuppressive therapies without treatment of the associated malignancy and to be alive at last follow-up. (J Am Acad Dermatol 2012;66:e55-65.)
• New-onset (biopsy-proven) CSVV within 12 months of new or recurrent solid-organ malignancy

• No other likely trigger for CSVV
  • Infection, drug (e.g. chemotherapy), autoimmune connective tissue disease

• Most common associated malignancies
  • Lung, breast, prostate, colon, renal

• The onset of CSVV may occur before, after, or concurrently with the malignancy

• CSVV may herald recurrence of malignancy
  • Three patients had CSVV in association with malignancy recurrence despite having no CSVV associated with their initial malignancy
IgA vasculitis and solid-organ malignancy

**Table I. Summary of characteristics of 47 previously reported patients with Henoch-Schönlein purpura associated with solid-organ malignancy**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean</td>
<td>62³</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>33 (70)</td>
</tr>
<tr>
<td>Type of solid-organ malignancy (n = 53)³, n (%)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>14 (26)</td>
</tr>
<tr>
<td>Prostate</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Kidney</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Gastric</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Breast</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Maxillary</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Cervical</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Colon</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Epiglottic, Hypopharyngeal</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Esophageal</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Anal, Rectal</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Ovarian, Endometrial</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Hepatocellular, Cholangiocarcinoma</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Onset of cutaneous vasculitis in relation to malignancy (n = 53)³, n (%)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>14 (26)</td>
</tr>
<tr>
<td>Synchronous⁴</td>
<td>19 (36)</td>
</tr>
<tr>
<td>After</td>
<td>20 (38)</td>
</tr>
</tbody>
</table>

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**Clinical Report**

**Henoch-Schönlein Purpura Associated With Solid-organ Malignancies: Three Case Reports and a Literature Review**

Josina O. PODIASEK, David A. WETTER, Mark R. PITTELKOW and David A. WADA
Department of Dermatology, Mayo Clinic, Rochester, MN, USA

Adult Henoch-Schönlein purpura (HSP) is rarely associated with solid-organ malignancies. We describe here three adult patients with HSP diagnosed within 3 months of the diagnosis of associated solid-organ malignancies, including pulmonary, prostate, and renal carcinomas. Two patients had complete remission with a combination of immunosuppressive therapies and treatment of the associated malignancy. The third patient had partial remission with immunosuppressive therapies, but never received treatment for the associated malignancy and did not achieve complete remission before his death 10 months after diagnosis of HSP. These cases suggest that HSP associated with solid-organ malignancies may be resistant to immunosuppressive therapies without treatment of the associated malignancy. Therefore, evaluation for solid-organ malignancies should be considered in adult patients without an identifiable cause of HSP, especially if the disease is not self-limited or does not respond appropriately to treatment. **Key words: coagulation; cutaneous vasculitis; malignancy.**
**Learning points**

- Solid-organ malignancy is a rare (but important) cause of CSVV (and subtypes including IgA vasculitis)
  - *Should consider in those with CSVV of unknown cause, and in those with chronic or recurrent CSVV not responding as expected to treatment*

- CSVV may herald recurrence of a previous malignancy
PRACTICE GAP #2

• Can skin biopsy findings (routine microscopy or direct immunofluorescence [DIF]) predict systemic disease in adult IgA vasculitis (Henoch-Schonlein Purpura)?
**Classification criteria of HSP – varied and challenging!**

**Most criteria emphasize the role of vascular IgA deposition in HSP**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>EULAR</td>
<td>Purpura or petechiae with lower limb predominance, plus at least one of the following: 1. Abdominal pain 2. LCV or proliferative glomerulonephritis with predominant IgA deposit 3. Arthritis/arthritis 4. Proteinuria or hematuria</td>
</tr>
<tr>
<td>ACR</td>
<td>At least two of the following: 1. Palpable purpura 2. Age ≤ 20 years at disease onset 3. Bowel angina or gastrointestinal bleeding 4. Wall granulocytes on biopsy Three or more criteria: HSP; two or fewer criteria: HY</td>
</tr>
<tr>
<td>Helder, De Castro, and Gibson</td>
<td>Three or more of the following criteria: 1. DIF results consistent with vascular IgA deposition 2. Patient age younger than 20 years 3. Gastrointestinal involvement 4. Upper respiratory tract infection (URI) prodrome 5. Mesangioproliferative glomerulonephritis with or without IgA deposition 6. Vasculitis, with IgA dominated immune deposits, affecting small vessels (ie, capillaries, venules, or arterioles) typically involves skin, gut, and glomeruli and is associated with arthralgias or arthritis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Vasculitis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large vessel vasculitis (LVV)</td>
<td>Takayasu arteritis (TAK) Giant cell arteritis (GCA)</td>
</tr>
<tr>
<td>Medium vessel vasculitis (MVV)</td>
<td>Polymyalgia rheumatica (PMR) Kawasaki disease (KD)</td>
</tr>
<tr>
<td>Small vessel vasculitis (SVV)</td>
<td>Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) Microscopic polyangiitis (MPA) Granulomatosis with polyangiitis (Wegener's) (GPA) Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Immune complex SVV Anti-glomerular basement membrane (anti-GBM) disease Cryoglobulinemic vasculitis (CV)</td>
</tr>
</tbody>
</table>

**IgA vasculitis (Henoch-Schönlein) (IgAV)**

IgA vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur.
Although IgA is *predominant* immunoreactant, other conjugates are often present on DIF in patients with HSP
Predictive factors for renal involvement in this study:

- **Purpura above the waist**
- Others: recent infectious history, fever, biological markers of inflammation
**Inclusion criteria:** 25 patients with palpable purpura of legs; skin biopsy showing LCV; and IgA deposition on DIF

**Exclusion criteria:** Coexisting malignancy, autoimmune disease, viral hepatitis, mixed cryoglobulinemia

*Important b/c non-HSP causes of IgA vasculitis include* multiple myeloma, SLE cryoglobulinemia, and IgA gammopathy (*Acta Derm Venereol 2012;92:388-392*)

**Results:** Significant association between IgM deposition on DIF and renal involvement ($P = .022$)

**Renal involvement:** Microscopic proteinuria, hematuria, or both appearing several times during 1 month f/u
What is our experience at Mayo Clinic in regards to DIF, histopathology, and correlates of systemic disease in adult HSP?
Correlates of systemic disease in adult Henoch-Schönlein purpura: A retrospective study of direct immunofluorescence and skin lesion distribution in 87 patients at Mayo Clinic

Timothy J. Poterucha, BS, David A. Wetter, MD, Lawrence E. Gibson, MD, Michael J. Camilleri, MD, and Christine M. Lohse, MS

Rochester, Minnesota

Background: Detection of IgM in lesional skin of adult patients with Henoch-Schönlein purpura via direct immunofluorescence (DIF) has been associated with the presence of renal disease.

Objective: We sought to examine whether DIF findings of skin biopsy specimens and distribution of skin lesions were associated with the presence of systemic disease, including renal, gastrointestinal tract, and joint involvement.

Methods: We performed a retrospective review of adult patients with Henoch-Schönlein purpura seen at Mayo Clinic between 1992 and 2011.

Results: Of the 87 patients (mean age, 46.1 years), 51 (59%) were male. A total of 39 patients (45%) had renal disease; 32 (37%), gastrointestinal tract involvement; 29 (43%), joint involvement; and 65 (75%), some systemic involvement. In all, 61 patients (70%) had cutaneous lesions above the waist. The DIF findings showed the presence of IgA in all 87 patients (100%). In addition, findings were positive for IgM in 32 patients (37%); IgG in 3 patients (3%); C3 in 75 patients (87%); and fibrinogen in 78 patients (92%). IgM was not found to be significantly associated with renal disease ($P = .10$); however, absence of fibrinogen was correlated with presence of renal involvement ($P = .04$). No other correlations were detected between DIF findings and systemic disease. Lesions above the waist were not significantly associated with renal ($P = .12$) or any ($P = .76$) systemic involvement.

Limitations: This study is retrospective.

Conclusions: Neither IgM in lesional skin nor distribution of skin lesions above the waist was a reliable indicator of renal or systemic disease in adults with Henoch-Schönlein purpura. (J Am Acad Dermatol 2012;67:612-6.)
***IgM on DIF was NOT significantly associated with renal involvement ($P = .10$)

*Absence of fibrinogen on DIF associated with renal involvement ($P = .04$) (only 7 of 85 pts tested negative – therefore unclear if clinically significant)

*No other conjugates (single or combination) were correlated with renal, joint, GI, or any systemic disease
*Lesions above the waist were NOT a predictor of renal ($P = .12$) or any systemic involvement ($P = .76$, data not shown)
Histopathology and correlates of systemic disease in adult Henoch-Schönlein purpura: A retrospective study of microscopic and clinical findings in 68 patients at Mayo Clinic

Timothy J. Poterucha, BS, a David A. Wetter, MD, b Lawrence E. Gibson, MD, b,c Michael J. Camilleri, MD, b,c and Christine M. Iohse, MS d

Rochester, Minnesota

Background: The histopathology of Henoch-Schönlein purpura (HSP) is well defined, but specific markers have not been correlated with systemic involvement.

Objective: We sought to evaluate whether histopathologic markers were associated with renal or other systemic involvement in adult HSP.

Methods: We retrospectively reviewed clinical information and pathology slides of 68 adult patients with HSP seen at Mayo Clinic between 1992 and 2011.

Results: Of the 68 patients, mean age was 45.8 years and 41 (60%) of the patients were male. Renal involvement was observed in 30 patients (44%), gastrointestinal tract in 27 (40%), joint in 32 (47%), and any systemic signs in 52 (76%). Patients who were older than 40 years and had leukocytoclastic vasculitis with an absence of eosinophils on skin biopsy specimen had higher rates of renal involvement than those who did not have both of these features (75% vs 27%; P < .001). Patients with skin biopsy specimens showing leukocytoclastic vasculitis and an absence of histiocytes had higher rates of gastrointestinal tract involvement (P = .03). Age of 40 years or younger was associated with increased risk for gastrointestinal tract involvement and a nonsignificant trend for joint involvement (P = .004 and P = .06, respectively).

Limitations: This study is retrospective, and the causative factors of HSP were unable to be determined in many patients.

Conclusion: Patients older than 40 years with HSP who had an absence of eosinophils on skin biopsy specimen had a nearly 3-times increased risk of renal involvement compared with patients who did not have both features. (J Am Acad Dermatol 2013;68:420-4.)
Mayo Study - Key Findings

- Leukocytoclastic vasculitis (LCV) with ABSENCE of eosinophils – more likely to have renal involvement ($P = .008$)
- Age >40 years – more likely to have renal involvement ($P = .03$)
Can Age and Eosinophils Together Predict Renal Involvement?

*Those with (1) LCV without eosinophils and (2) age >40 years had 75% rate of renal disease (18 of 24 pts) vs. 27% (12 of 44) for all other pts ($P = <.001$)

- **A NEARLY 3-TIMES INCREASED RISK!**

*Combination of these 2 features (age >40; absence of eosinophils on skin biopsy) may be useful renal risk stratification tool when evaluating adults with HSP.*

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**Table III. Rate of renal involvement as function of both tissue eosinophils and age**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Histopathologic findings</th>
<th>Patients, No.</th>
<th>Patients with renal involvement, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 40</td>
<td>LCV with eosinophils</td>
<td>17</td>
<td>5 (29)</td>
</tr>
<tr>
<td>≤ 40</td>
<td>LCV without eosinophils</td>
<td>9</td>
<td>2 (22)</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>LCV with eosinophils</td>
<td>18</td>
<td>5 (28)</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>LCV without eosinophils</td>
<td>24</td>
<td>18 (75)*</td>
</tr>
</tbody>
</table>

LCV, Leukocytoclastic vasculitis.

*Rate of renal involvement in subgroup with age older than 40 years and with absence of tissue eosinophils is statistically different from all other patients combined ($P < .001$).
Why Would Eosinophils “Protect” Against Renal Disease?

• Perhaps tissue eosinophils indicate drug-induced etiology?
  • Tissue eosinophils observed in drug-induced CSVV (1)
  • Lower rate of renal disease in drug-induced vasculitis (2,3)

• We were unable to test this hypothesis – unable to determine cause in most of our pts (50/68)

(2) Garcia-Porrúa et al. J Rheumatol 1999;26:1942-4
*Learning points*

• (1) Various classification criteria for HSP – vascular IgA deposition is central to most

• (2) HSP often demonstrates multiple conjugates on DIF

• (3) IgM in lesional skin was NOT significantly associated with renal disease in adult HSP

• (4) Lesion distribution above the waist did NOT predict renal disease in adult HSP

• (5) Patients >40 years of age with HSP who had absence of eosinophils on skin biopsy – nearly 3-times increased risk of renal involvement
PRACTICE GAP #3

- Can “biologic” medications (such as tumor necrosis factor–alpha [TNF-α] inhibitors) that are used to treat rheumatologic skin conditions ACTUALLY CAUSE cutaneous vasculitis?
Cutaneous side effects of anti–tumor necrosis factor biologic therapy: A clinical review

Aikaterini-Evaggelia Moustou, MD, Athina Matakovits, MD, Clio Dessinioti, MD, Christina Antoniou, MD, Petros P. Sifakis, MD, and Alexander J. Stratigos, MD

Athens, Greece

Background: Anti-tumor necrosis factor (anti-TNF) biologic agents have been associated with a number of adverse events.

Objective: To review the cutaneous reactions that have been reported in patients receiving anti-TNF therapy.

Methods: We performed a systematic MEDLINE search of relevant publications, including case reports and case series.

Results: Reported cutaneous events included infusion and injection site reactions, psoriasiform eruptions, lupus-like disorders, vasculitis, granulomatous reactions, cutaneous infections, and cutaneous neoplasms. Infusion reactions and injection site reactions were definitely associated with anti-TNF administration, whereas all other events had a varying strength of association and severity, not necessarily requiring drug discontinuation.

Limitations: Most information was derived from spontaneous case reports, where ascertainment biases and frequency of reporting may impair detection methodology and causal relationships.

Conclusions: As anti-TNF biologic agents are progressively being used in clinical practice, cutaneous adverse events will be encountered more frequently. Until more data are accumulated with respect to their pathogenesis and potential association with anti-TNF therapy, dermatologists should become more familiar with the clinical presentation and management of such events. (J Am Acad Dermatol 2009;61:486-504.)
Cutaneous side-effects of anti-TNF agents

- Infusion reaction
- Injection site reaction
- Psoriasis and psoriasiform eruptions
- Eczema/dermatitis
- Lichenoid reactions
- Vasculitis (LCV)
- Lupus erythematosus
- Granulomatous reactions
- Cutaneous infections
- Cutaneous lymphoma
- Non-melanoma skin cancer
- Dermatomyositis
Autoimmune diseases induced by biological agents
A double-edged sword?

Manuel Ramos-Casals a,*, Roberto-Perez-Alvarez b, Candido Diaz-Lagares a, Maria-Jose Cuadrado c, Munther A. Khamashta c
and BIOGEAS Study Group 1

ABSTRACT

Biological agents are increasingly used for a rapidly-expanding number of rheumatic and systemic autoimmune diseases, with a growing number of reports of the paradoxical induction of autoimmune processes, overwhelmingly associated with anti-TNF agents. In this review, we analyze the clinical characteristics and outcomes of autoimmune diseases developing after biological therapies through a baseline Medline search as one of the objectives of the BIOGEAS project, created by the Spanish Society of Internal Medicine. The latest update of our registry (15 July 2009) included more than 800 cases of autoimmune diseases secondary to biological therapies, including a wide variety of both systemic (lupus, vasculitis, sarcoidosis and antiphospholipid syndrome) and organ-specific (interstitial lung disease, uveitis, optic neuritis, peripheral neuropathies, multiple sclerosis and autoimmune hepatitis) autoimmune processes. The majority of cases appeared between one month and one year after initiation of the biological agent and complete resolution was observed in nearly 75% of cases after cessation of therapy. The induced autoimmune diseases with the poorest outcomes were interstitial lung disease, inflammatory ocular disease and central nervous system demyelinating diseases.

Classification of autoimmune diseases induced by biological agents

2.1. Systemic lupus erythematosus
2.2. Vasculitis
2.3. Sarcoidosis
2.4. Antiphospholipid syndrome and related features
2.5. Demyelinating neurological diseases
  2.5.1. Demyelinating CNS involvement
  2.5.2. Demyelinating peripheral neuropathies
2.6. Interstitial lung disease
2.7. Inflammatory ocular diseases
2.8. Autoimmune hepatitis
2.9. Psoriasis
2.10. Other autoimmune diseases
ILLUSTRATIVE CASE

- 64 year-old man with CSVV
- Had rheumatoid arthritis (RA), well-controlled on infliximab for 5 years
- Workup negative for systemic involvement; and associated triggers (infection, malignancy, autoimmune disease, other drug)
- Rheumatologic evaluation confirmed quiescence of RA
- Diagnosis: **Vasculitis associated with anti-TNF therapy**; partial response 1 month after stopping infliximab and starting prednisone and hydroxychloroquine
What is the Mayo Clinic experience with vasculitis associated with TNF-α inhibitors?
Vasculitis Associated With Tumor Necrosis Factor-α Inhibitors

Olayemi Sokumbi, MD; David A. Wetter, MD; Ashima Makol, MBBS; and Kenneth J. Warrington, MD

Abstract

Objective: To describe the clinical characteristics, histopathologic features, and outcomes of patients in whom vasculitis developed in association with use of tumor necrosis factor-α (TNF-α) inhibitors.

Patients and Methods: This is a retrospective review of patients evaluated at Mayo Clinic, Rochester, Minnesota, from January 1, 1998, through March 31, 2011, with a diagnosis of vasculitis induced by anti–TNF-α therapy.

Results: Of 8 patients with vasculitis associated with anti–TNF-α therapy (mean age, 48.5 years), 6 (75%) were female. Four (50%) had rheumatoid arthritis, 1 (13%) had Crohn disease, and 3 (38%) had ulcerative colitis. Five (63%) were treated with infliximab, 2 (25%) with etanercept, and 1 (13%) with adalimumab. The mean duration of treatment before development of vasculitis was 34.5 months. The skin was the predominant organ affected (5 patients [63%]), with the most common cutaneous lesion being palpable purpura (4 of 5 [80%]). Two organs involved in systemic vasculitis were the peripheral nervous system (4 patients [50%]) and kidney (1 patient [13%]). All cases of vasculitis were histopathologically confirmed. Seven of 8 patients improved with discontinuation of therapy (mean time to resolution, 6.9 months) and adjuvant treatment (all 8 received prednisone; another agent was also used in 7); rechallenge with anti–TNF-α therapy was not attempted in any patient. At last follow-up, no patients had experienced a recurrence of vasculitis after therapy discontinuation.

Conclusion: Cutaneous small-vessel vasculitis was the most common finding, but systemic vasculitis, including peripheral nerve and renal vasculitis, was also frequently observed.
Mayo Study – Key Points

- 34.5 months of anti-TNF therapy (mean)
- 5 skin, 4 nerve, 1 kidney
- 6.9 months to resolve (mean)
- No patients rechallenged with alternate anti-TNF agent
Can patients be switched to an alternative TNF-α inhibitor without recurrence of vasculitis?

6 of 9 patients (67%) rechallenged with the **SAME** agent had relapse of vasculitis

3 of 9 patients (33%) switched to **ALTERNATIVE** agent had relapse of vasculitis
*Learning points*

- Anti-TNF-α therapy can be associated with drug-induced autoimmune diseases, including cutaneous vasculitis.

- May have long latency period from drug initiation to development of vasculitis (our study had mean time of 34.5 mos [range, 2-72 mos]).

- Need to confirm quiescence of underlying disease being treated (e.g. RA) before attributing to anti-TNF therapy.
  - Since RA and inflammatory bowel disease (IBD) can both cause vasculitis.

- Safety of rechallenging with an alternative anti-TNF agent remains unclear.
PRACTICE GAP #4

• Can (and how often does) antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis present with skin lesions?
Epidemiology of LCV

• True population-based incidence is unknown

• Estimated to be between 15 and 30 cases per million population per year (Chung et al, Cutaneous Vasculitis, In: Bolognia et al (eds), Dermatology, 2nd ed, 2008)

• Other studies:

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Study location</th>
<th>Duration of the study (y)</th>
<th>Population based</th>
<th>Incidence (cases per million population per year)</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>Olmsted County, MN</td>
<td>15</td>
<td>Yes</td>
<td>45</td>
<td>Only cutaneous biopsy-proven cases were included</td>
</tr>
<tr>
<td>Watts et al, 1998</td>
<td>Single district hospital, United Kingdom</td>
<td>4</td>
<td>No</td>
<td>38.6 (“Cutaneous vasculitis”)</td>
<td>Incidence was 15.4 cases per million population per year for “cutaneous leukocytoclastic angiitis”</td>
</tr>
<tr>
<td>Garcia-Pomua and Gonzalez-Gay, 1999</td>
<td>Primary referral center in a region of northwest Spain</td>
<td>9</td>
<td>No</td>
<td>29.7</td>
<td>Incidence calculated for cases of “hypersensitivity vasculitis”</td>
</tr>
</tbody>
</table>

The Rochester Epidemiology Project (REP) is a comprehensive database that links medical records of virtually all Olmsted County, Minnesota (MN), residents at different medical facilities in Olmsted County (including outpatient clinics, inpatient hospitals, and nursing homes or at autopsies).

- Allows for population-based epidemiologic research to be performed on numerous conditions including rheumatic skin diseases.
How to Bridge the “LCV Epidemiology Gap” in the Literature?

- Use the REP to determine the population-based incidence of LCV and its subtypes
  - CSVV
  - IgA vasculitis
  - Urticarial vasculitis
  - ANCA-associated vasculitis
  - Cryoglobulinemic vasculitis
Incidence of Leukocytoclastic Vasculitis, 1996 to 2010: A Population-Based Study in Olmsted County, Minnesota

Amrita Arora, MD; David A. Wetter, MD; Tania M. Gonzalez-Santiago, MD; Mark D.P. Davis, MD; and Christine M. Lohse, MS

Abstract

Objective: To determine the population-based incidence of leukocytoclastic vasculitis (LCV).

Patients and Methods: This is a retrospective population-based study of all Olmsted County, Minnesota, residents with a skin biopsy—proven diagnosis of LCV from January 1, 1996, through December 31, 2010.

Results: A total of 84 patients (mean age at diagnosis, 48.3 years) with newly diagnosed skin biopsy—proven LCV (43 women and 41 men) were identified. The incidence rate (age and sex adjusted to the 2000 US white population) was 4.5 per 100,000 person-years (95% CI, 3.5-5.4). The incidence of LCV increased significantly with age at diagnosis (P<.001) and did not differ between female and male patients. Subtypes of LCV were cutaneous small-vessel vasculitis (CSVV), 38 patients (45%); IgA vasculitis, 25 (30%); urticarial vasculitis, 10 (12%); cryoglobulinemic vasculitis, 3 (4%); and antineutrophil cytoplasmic antibody—associated vasculitis, 8 (10%). LCV was idiopathic in 29 of 38 patients with CSVV (76%) and 24 of 25 patients with IgA vasculitis (96%). Thirty-nine of 84 patients (46%) had systemic involvement, with the renal system most commonly involved (17 of 39 [44%]). Twenty-four of 80 patients (30%) with follow-up data available had recurrent disease. Compared with the Minnesota white population, observed survival in the incident LCV cohort was significantly poorer than expected (P<.001), including the subset of patients with idiopathic CSVV (P=.03).

Conclusion: The incidence of LCV was higher than that reported in previously published studies. Idiopathic LCV was more common in our population-based cohort than that described previously. Overall survival was significantly poorer (P<.001) and should be explored further in future studies.
Mayo Study Inclusion Criteria

• (1) Final diagnosis of cutaneous vasculitis rendered by clinician

• (2) Diagnosis confirmed by histopathologic findings of LCV on skin biopsy

• (3) Incident cases of LCV (i.e. first lifetime diagnosis of LCV) in which patients were residents of Olmsted County, MN, for at least 1 year before and 1 year after the date of diagnosis
Frequency of LCV Subtypes (including ANCA-associated)

- CSVV most common (45%), followed by IgA vasculitis (30%)

**Note that 10% of patients had ANCA-associated vasculitis** – highlighting the importance of assessing for this type of systemic vasculitis in all patients with clinical vasculitis who present with LCV on skin biopsy
Mayo Study - Epidemiology of LCV

- Overall (age- and sex-adjusted) incidence of LCV: 4.5 per 100,000 person-years (45 cases per million population per year)
Key Points (Epidemiology of LCV)

• Our population-based study showed the incidence to be 1.5 to 3 times higher than what is reported in textbooks (BRIDGING A PRACTICE GAP)

• Practical message: How common is LCV? Slightly more common than cutaneous lupus (which has an incidence of 43 cases per million per year; Arch Dermatol. 2009;145(3):249-253)

Incidence of Cutaneous Lupus Erythematosus, 1965-2005

A Population-Based Study

Olayemi Durosaro, BS; Mark D. P. Davis, MD; Kurtis B. Reed, BS; Audrey L. Rohlinger, BS
What is the most common cutaneous manifestation of granulomatosi...
Mayo Study – GPA Cutaneous Findings

Cutaneous Wegener’s granulomatosis: Clinical, histopathologic, and immunopathologic features of thirty patients

Mazen S. Daouad, MD,a Lawrence E. Gibson, MD,a Richard A. DeRemee, MD,b Ulrich Specks, MD,b Rokea A. el-Azhary, MD,4 and W. P. Daniel Sa, MDa Rochester, Minnesota, and Jacksonville, Florida

Background: Wegener’s granulomatosis (WG) is a systemic disease characterized by necrotizing granulomatous inflammation and vasculitis. Its cutaneous manifestations vary.

Objectives: We reviewed and characterized the clinical, pathologic, and immunopathologic features of the specific cutaneous manifestations of WG and investigated the sensitivity and the specificity of anti-neutrophilic cytoplasmic antibody (c-ANCA) in the cutaneous manifestations of this disease.

Methods: A retrospective analysis was conducted of 244 cases of WG observed between 1988 and 1992.

Results: Skin involvement occurred in 14% of the patients and was more frequent in generalized WG. Skin lesions may be an early premonitory sign of renal disease. Necrotizing ulcerations resembling pyoderma gangrenosum were not uncommon. leukocytoclastic vasculitis was the most common cutaneous pathologic pattern. Findings of c-ANCA were positive in 81% of patients with cutaneous WG.

Conclusion: Skin involvement usually occurred at presentation with generalized disease. c-ANCA is a valuable adjunct to diagnosis and follow-up of WG. (J Am Acad Dermatol 1994;31:605-12.)

- Nearly one-half of patients with cutaneous GPA had palpable purpura
- LCV most common skin biopsy finding
- “Pyoderma-like ulcer” also common

Table II. Clinical, histopathologic, and c-ANCA findings in 30 patients with cutaneous WG

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable purpura</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Pyoderma-like ulcer</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Papule</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Nodules</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Superficial ulcerations</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Bullae</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Maculae and erythema</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

Location
- Lower extremities: 23 (76)
- Upper extremities: 11 (35)
- Trunk: 3 (9)
- Head and neck: 2 (6)

Biopsy findings
- Leukocytoclastic vasculitis: 24 (80)
- Extravascular granuloma: 3 (10)
- Mixed inflammatory pattern: 5 (16)
- Positive c-ANCA result: 25 (83)
- CNS disease: 14 (47)
- Renal disease: 24 (80)
- Ocular disease: 9 (30)
Granulomatosi with polyangiitis (GPA) can manifest in the skin as pyoderma gangrenosum (PG)-like ulcerations.

If “PG” on face/ears – consider GPA

Pyoderma-gangrenosum-like lesions in GPA

Pyoderma-gangrenosum-like lesions are a characteristic feature of GPA and may appear on the face. This feature usually does not occur in other types of ANCA-associated vasculitis [12, 13]. Histopathology is characterized by a palisaded granuloma surrounding a large central zone of a geographic necrosis, with marked neutrophilic abscess formation and hemorrhage.

PG-like ulcerations of legs due to GPA (patient cared for by my colleague, Mark Davis, M.D.)
Recent Mayo Study – GPA in Children

Cutaneous manifestations of pediatric granulomatosis with polyangiitis: A clinicopathologic and immunopathologic analysis

Adam C. Wright, MD,* Lawrence E. Gibson, MD,†,‡ and Dawn Marie R. Davis, MD* Rochester, Minnesota

Background: Granulomatosis with polyangiitis (GPA) is a rare systemic vasculitis associated with variable cutaneous manifestations and histopathologic findings. It is less frequent in children than adults and is often positive for cytoplasmic antineutrophil cytoplasmic antibody (ANCA) or proteinase 3-ANCA.

Objective: We sought to better define and correlate the clinical, histopathologic, and immunopathologic characteristics of cutaneous GPA in pediatric patients.

Methods: We retrospectively reviewed clinical records and cutaneous histopathologic specimens of patients 17 years or younger with cutaneous manifestations of GPA who were seen at our institution from 1990 to 2013.

Results: Of the 52 patients identified with GPA, cutaneous involvement occurred in 36.5% and was the initial manifestation of disease in 7.7%. Of the 19 patients with cutaneous involvement, 26.3% developed acneiform and folliculitis-like papules; 84.2% were cytoplasmic ANCA positive; and 78.9% were proteinase 3-ANCA positive. Histopathologic features included leukocytoclastic vasculitis, granulomatous inflammation, acneiform and perifollicular inflammation, granulomatous vasculitis, and palisading granulomas.

Limitations: Our study was limited because of its retrospective design.

Conclusion: Pediatric patients with cutaneous GPA most commonly have palpable purpura, leukocytoclastic vasculitis, and positive cytoplasmic ANCA or proteinase 3-ANCA serologic results. Cutaneous manifestations and histopathologic findings vary, but acneiform lesions may be a cutaneous manifestation of the disease unique to this age group. (J Am Acad Dermatol 2015;72:859-67.)

Capsule Summary

- Pediatric patients with granulomatosis with polyangiitis commonly have palpable purpura, leukocytoclastic vasculitis, and positive serologic testing for cytoplasmic antineutrophil cytoplasmic antibody or proteinase 3-antineutrophil cytoplasmic antibody.
- Acneiform lesions representative of granulomatosis with polyangiitis may be a unique cutaneous finding in this population.
- Understanding the histopathologic and cutaneous characteristics of granulomatosis with polyangiitis in pediatric patients may aid in diagnosis.

Acneiform and folliculitisle-like papules were identified in over one-quarter of patients (5 of 19) with cutaneous findings of GPA.
*Learning points*

- ANCA-associated vasculitis may present with skin lesions
- **Palpable purpura** is the most common skin manifestation of ANCA-associated vasculitis (including GPA)
- In a population-based cohort, **ANCA-associated vasculitis represents 10% of all cases of LCV**
  - Thus include ANCA testing in your evaluation of patients with LCV
- Keep GPA in the differential diagnosis of **PG-like ulcerations**
  - Particularly if uncommon location such as the head/neck
- **Acneiform lesions** may be a unique cutaneous finding in GPA in children
SUMMARY (TAKE HOME MESSAGES)

• Solid-organ malignancy is a rare (but important) cause of CSVV
• Skin biopsy findings may help predict risk of renal disease in IgA vasculitis (HSP)
• Anti-TNF-α therapy can induce cutaneous vasculitis (even after months to years of treatment)
• Palpable purpura (histopathologic correlate: LCV) is the most common skin manifestation of ANCA-associated vasculitis
  • 10% of patients with LCV in population-based (community) setting will have ANCA-associated vasculitis

• Practical approach to diagnosis, evaluation, and management of CSVV (see Am J Clin Dermatol article)
EPILOGUE - My Approach to CSVV

A Practical Approach to the Diagnosis, Evaluation, and Management of Cutaneous Small-Vessel Vasculitis

Megan R. Goeser · Valerie Laniosz · David A. Wetter

CSVV
- Does not fulfill criteria for a distinct subtype of LCV (see entities below)
- Synonyms: “leukocytoclastic angiitis,” “hypersensitivity vasculitis”

IgA vasculitis

Urticarial vasculitis

ANCA-associated vasculitis

Cryoglobulinemic vasculitis

Infection

Medication

Autoimmune connective tissue disease
- Lupus erythematosus
- Rheumatoid arthritis
- Sjögren syndrome

Inflammatory conditions
- Inflammatory bowel disease
- Cryoglobulinaemia (types II and III)
- Anti-neutrophil cytoplasmic antibody-associated vasculitis
- Behçet disease

Infection
- *Streptococcus pyogenes*
- Hepatitis B and C virus
- Human immunodeficiency virus

Medication
- Antibiotics (β-lactams [penicillin, cephalosporins], sulfa drugs, minocycline)
- Non steroidal anti-inflammatory drugs
- Granulocyte macrophage colony-stimulating factor
- Propylthiouracil
- Tumor necrosis factor-α antagonists
- Levamisole-tainted cocaine

Malignancy
- Hematologic
- Solid organ

Data from Russell and Gibson [4]
Example of organized approach “in action”

- Subtypes of LCV
- Categories of LCV causes beneath EACH subtype of LCV
3 key questions to ask in the diagnosis and evaluation of cutaneous vasculitis
Three Key Questions

• (1) Is the morphology of the cutaneous eruption consistent with vasculitis?

• (2) Does the patient have any symptoms or signs suggestive of extracutaneous involvement of vasculitis?

• (3) Are there any identifiable etiologies or systemic disease associations for vasculitis?
**Purpura**

**Petechial or Macular (<1cm) (non-palpable)**
- Thrombocytopenia
- Abnormal platelet function
- ↑ intravascular pressure
- Pigmented purpuric dermatosis
- Small vessel vasculitis (a few lesions should be palpable)

**Ecchymotic**
- Coagulation defect
  - Hemophilia
  - Anticoagulants
  - Liver disease
  - ↓ Vitamin K
- Decreased support of dermal vessels
  - Actinic damage
  - Corticosteroids
  - Amyloidosis
  - ↓ Vitamin C
- Collagen disorder
  - Ehlers-Danlos

**Inflammatory (erythema present), Round (Some are palpable)**
- Vasculitis (small vessel)
  - Hypersensitivity
  - HSP/IgA vasculitis
  - Cryoglobulinemia (mixed)
- ANCA-associated
- Connective tissue disease-associated
- Lichenoid conditions
- PLEVA
- Erythema multiforme
- If targetoid – IgA vasculitis or erythema multiforme

**Retiform**
- Inflammatory
  - IgA vasculitis
- ANCA-associated
- Connective tissue disease-associated
- Non-inflammatory
  - Cryoglobulinemia (monoclonal)
  - Antiphospholipid Abs
  - Calciphenesis
  - Warfarin necrosis
  - Heparin necrosis
  - DIC
  - Hypercoagulable state
  - Embolic condition
  - Livedoid vasculopathy
  - Angioinvasive infection
  - Cocaine

Fig. 6.7 Algorithm for approaching the patient with purpura (Adapted from Refs. [1–3])
Answer question #1 through skin biopsy (routine microscopy and DIF)

A

Is the morphology of the eruption consistent with vasculitis (ie, palpable purpura)?

- Yes
  - Typically obtain biopsy sample for H&E and DIF
  - Pertinent positives
    - H&E
      - Granulomatous vasculitis: systemic
      - Lymphocytic vasculitis: CTD, viral infection, drug
      - Small- and medium-vessel involvement: ANCA or CTD
      - Urticarial vasculitis with dermal interstitial neutrophilic infiltrate: hypocomplementemic urticarial vasculitis (consider SLE)
      - **HSP without eosinophils in patients >40 years old: renal involvement**
    - DIF
      - IgA predominant: HSP
      - Prominent IgM: cryoglobulin or rheumatoid vasculitis
      - Positive around vessels and BMZ: hypocomplementemic urticarial vasculitis (consider SLE)
      - Negative: pauci-immune vasculitis (ie, ANCA-associated)

- No
  - Consider alternative diagnoses:
    - Thrombocytopenia
    - Abnormal platelet function
    - Pigmented purpuric dermatosis
    - Coagulation defect
    - Increased vascular pressure or weak dermal vessels
    - Collagen disorders
    - Lichenoid disorders
    - Calciphylaxis
    - Warfarin or heparin necrosis
    - Embolism
    - Angioinvasive infection

Answer questions 2 and 3 through review of systems, exam, and laboratory tests (see highlighted boxes below)

<table>
<thead>
<tr>
<th>Type of evaluation</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td>Clear inciting factor in isolated episode, with no suggestion of underlying internal organ involvement or associated systemic disorder</td>
</tr>
<tr>
<td>More extensive</td>
<td>Chronic or recurrent disease, unclear cause, history and physical examination suggest underlying internal organ involvement or associated systemic disorder</td>
</tr>
</tbody>
</table>

Laboratory tests

- Complete blood count with differential
- Creatinine
- Sedimentation rate
- Liver function tests
- Urinalysis
- Limited workup PLUS
- Hepatitis B and C serology
- Streptococcal antibodies
- Human immunodeficiency virus antibody
- Antinuclear antibody
- Extractable nuclear antigen
- Rheumatoid factor
- Complement levels (C3, C4, total)
- Cryoglobulins
- Serum monoclonal protein study (protein electrophoresis and immunofixation)
- Peripheral blood smear
- Antineutrophil cytoplasmic antibodies
- Chest radiography
- Stool guaiac
- Other tests based on concern for specific organ involvement, malignancy, etc.

Signs of systemic involvement of the vasculitis, based on review of systems [18]
- Constitutional: fever, weight loss, fatigue
- Musculoskeletal: arthralgias, myalgias
- Renal: hematuria
- Gastroenterologic: abdominal pain, bloody stools
- Neurologic: numbness, paraesthesias, weakness
- Cardiopulmonary: shortness of breath, chest pain, cough, hemoptysis
- Ear/Nose/Throat: sinusitis

Any clear inciting factors for vasculitis? (Table 1)
- Yes
- No

Limited laboratory evaluation for systemic involvement:
- Complete blood count
- Creatinine
- Sedimentation rate
- Liver function testing
- Urinalysis

First episode?
- Yes
- No

Extensive laboratory evaluation (Table 2)

4 Key Treatment Principles

• (1) Is it an isolated single episode of vasculitis, or a chronic/recurrent condition?
• (2) Is there an identifiable cause of the vasculitis (e.g. drug, infection, underlying systemic disorder)?
• (3) Is there systemic (internal organ) involvement of the vasculitis?
• (4) How severe is the cutaneous involvement?
<table>
<thead>
<tr>
<th>Type of cutaneous vasculitis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single episode</td>
<td>Remove inciting cause (if any identified)</td>
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<tr>
<td></td>
<td>Symptom alleviation</td>
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<tr>
<td></td>
<td>Bed rest, leg elevation, compression stocking, oral antihistamines, topical corticosteroids, nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td></td>
<td>Consider short taper of prednisone (40–60 mg daily for 4–6 weeks) for widespread, severely symptomatic, or ulcerative or necrotic disease</td>
</tr>
<tr>
<td>Chronic and idiopathic</td>
<td>First-line</td>
</tr>
<tr>
<td></td>
<td>Colchicine (0.6 mg 2–3 times daily)</td>
</tr>
<tr>
<td></td>
<td>Dapsone (100–200 mg daily) (obtain glucose-6-phosphate dehydrogenase level before therapy)</td>
</tr>
<tr>
<td></td>
<td>Combination colchicine and dapsone</td>
</tr>
<tr>
<td></td>
<td>Second-line</td>
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<tr>
<td></td>
<td>Mycophenolate mofetil (2–3 g daily, in divided doses)</td>
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<tr>
<td></td>
<td>Azathioprine (2–2.5 mg/kg daily if thiopurine methyltransferase levels are normal)</td>
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<td></td>
<td>Methotrexate (10–25 mg weekly; however, may cause cutaneous vasculitis [4])</td>
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<tr>
<td></td>
<td>Short tapering course of prednisone over 2–3 months while initiating corticosteroid-sparing agent</td>
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<tr>
<td>Refractory (unresponsive to above treatment)</td>
<td>Hydroxychloroquine (400 mg daily; only for urticarial vasculitis)</td>
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<td></td>
<td>Intravenous immunoglobulin (2 g/kg monthly, divided over 2–4 days)</td>
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<td></td>
<td>Rituximab (1 g, intravenous, on days 1 and 15)</td>
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<td></td>
<td>Cyclosporine (2.5–5 mg/kg daily, in divided doses; short-term use in severe disease)</td>
</tr>
</tbody>
</table>

**Overarching treatment guidelines**

1. Treat underlying cause of vasculitis (if identified)

2. Other treatment options depend upon whether vasculitis is:
   - Isolated or recurrent
   - Widespread or symptomatic
   - Associated with systemic involvement

Questions & Discussion