Adult Henoch-Schönlein Purpura in a Patient With Myelodysplastic Syndrome and a History of Follicular Lymphoma

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GOAL

To understand Henoch-Schönlein purpura (HSP) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the criteria for diagnosing HSP.
2. Explain the association of malignancy and HSP.
3. Discuss the prevalence of HSP in adults.

CME Test on page 138.

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Henoch-Schönlein purpura (HSP) is a systemic leukocytoclastic vasculitis involving arterioles and venules most commonly in the skin, glomeruli, and gastrointestinal tract. In skin, it is associated with IgA deposition around dermal blood vessels. While an exact cause of HSP has not been elucidated, several processes have been implicated in its development, including infections; drugs; and allergic, rheumatologic, and neoplastic diseases. We present a 57-year-old woman with a history of follicular lymphoma who developed HSP likely associated with myelodysplastic syndrome. This case is clinically significant because the patient was thought to be in remission of her hematologic disease until her skin findings prompted further evaluation. Her diagnosis of HSP was based on clinical presentation with palpable purpura and abdominal pain, and was confirmed with biopsy and immunohistochemical analyses of purpuric

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papules demonstrating leukocytoclastic vasculitis and strong anti-IgA labeling in the dermal endothelial cells consistent with immunocomplex deposition. The occurrence of vasculitis and malignant disease in the same patient often is difficult to interpret, as some patients may exhibit both diseases independently and by chance, while others may have vasculitis as a paraneoplastic syndrome. We review cases of adult HSP associated with malignancy in the literature.

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Case Report

A 57-year-old woman with a history of follicular lymphoma in complete remission presented to the dermatology clinic with a 3-week history of a new asymptomatic erythematous rash distributed across her arms, legs, and buttocks. She denied the use of any new medications but did report resuming use of pilocarpine 3 months prior to presentation and ursodiol 2 months prior to presentation. She had previously taken both of these medications without adverse effects. On initial presentation, the patient denied fever, chills, nausea, vomiting, dyspnea, arthralgia, or myalgia. She denied any upper respiratory tract symptoms or preceding viral illness.

The patient's prior medical history included diabetes mellitus, hypertension, follicular lymphoma in remission, and severe chemotherapy-induced peripheral neuropathy. Her follicular lymphoma initially was treated with chemotherapy. She relapsed and was treated with an allogeneic bone marrow–derived stem cell transplant from an HLA antigen–identical sister approximately 9 years prior to presentation. The patient's medications included pilocarpine, ursodiol, a fentanyl citrate patch, gabapentin, nortriptyline, duloxetine, clonidine hydrochloride, magnesium oxide, methylphenidate hydrochloride, metformin, and glyburide. She reported no known drug allergies.

Full cutaneous examination revealed nonblanching erythematous macules and papules on the bilateral lower extremities, with scattered macules and papules on the upper arms, abdomen, and buttocks. Results of a punch biopsy showed a predominant perivascular infiltrate of lymphocytes, neutrophils, and eosinophils. There was focal endothelial swelling with mural fibrin deposits, extravasation of red blood cells, and rare necrotic keratinocytes consistent with leukocytoclastic vasculitis (Figure 1). Triamcinolone acetonide cream 0.1% was prescribed pending laboratory evaluation, which ultimately revealed a negative antinuclear antibody, negative rheumatoid factor, white blood cell count of 4.2 k/μL (reference range, 4–11 k/μL), hemoglobin level of 7.8 g/dL (reference range, 12–16 g/dL), and platelet count of 192 k/μL (reference range, 140–440 k/μL). A urinalysis was negative for red blood cells, proteins, and nitrites, but did show small leukocyte esterase and 5 to 10 white blood cells per high-power field.

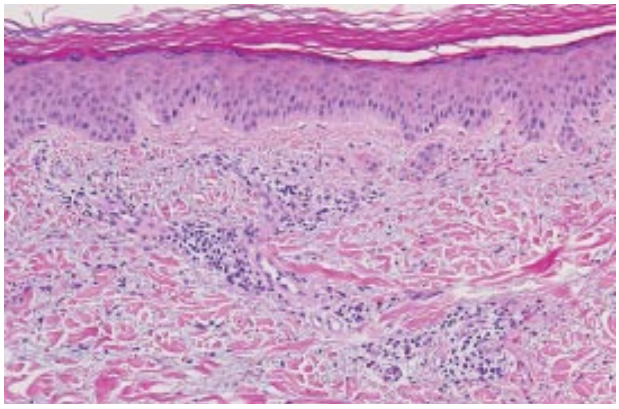

Figure 1. Mixed perivascular infiltrate containing lymphocytes, neutrophils, and eosinophils involving the superficial vascular plexus. The leukocytoclasia, extravasated erythrocytes, and vascular changes, including endothelial swelling and fibrinous change in the wall, are evidence of a vasculitic process (H&E, original magnification ×100).

Two weeks later, the patient complained of crampy abdominal pain (requiring morphine); decreased appetite; weakness; headache, as well as nausea; and extension of the eruption to involve her arms, legs, and entire trunk. She denied melena, hematochezia, and any urinary tract symptoms. Physical examination revealed diffuse tenderness in the epigastric area and a nonpalpable liver and spleen. Full cutaneous examination showed hemorrhagic bullae on the patient's lower extremities (Figure 2) and palpable purpura on her arms. Since the initial presentation 2 months prior, the patient's hematocrit level had dropped approximately 10% from 34.6% to 24.3% (reference range, 41.0%–50.0%). Her white blood cell count was slightly lower (3.6 k/μL) and her platelet count was 144 k/μL. Of note, her D-dimer level was elevated (1846 ng/mL; reference range, 0–230 ng/mL), as was her fibrinogen level (613 mg/dL; reference range, 220–530 mg/dL). Repeat urinalysis showed no proteinuria, hematuria, or nitrites.

The patient subsequently was admitted to the hospital. A workup of her gastrointestinal tract, including a computed tomographic scan of the abdomen and endoscopy, failed to show an etiology for the abdominal pain. Her amylase and lipase levels were normal, and stool cultures and guaiac occult blood tests were negative. Biopsies performed during endoscopy showed mild acute colitis of the hepatic

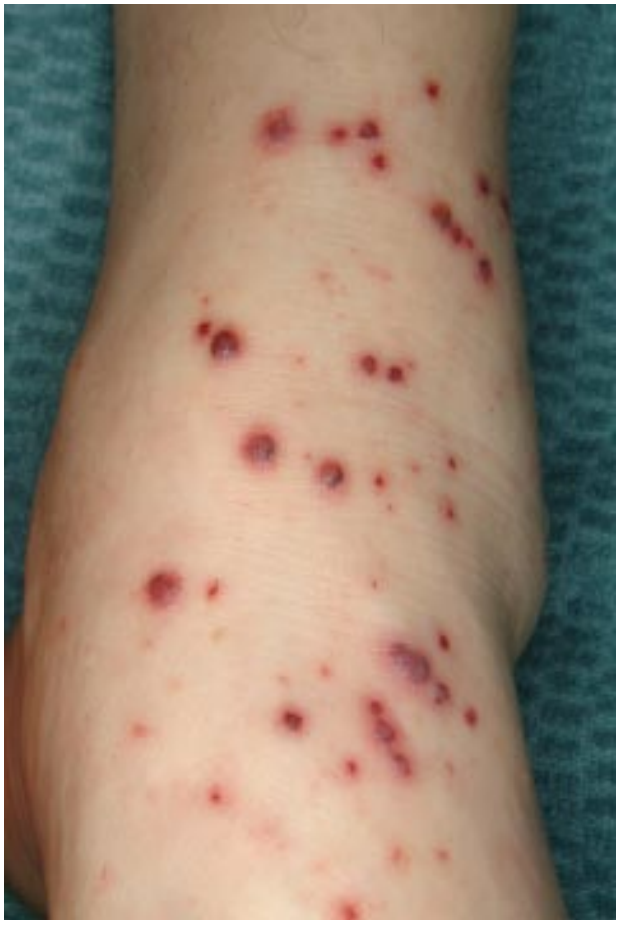

Figure 2. Hemorrhagic bullae of the lower extremity.

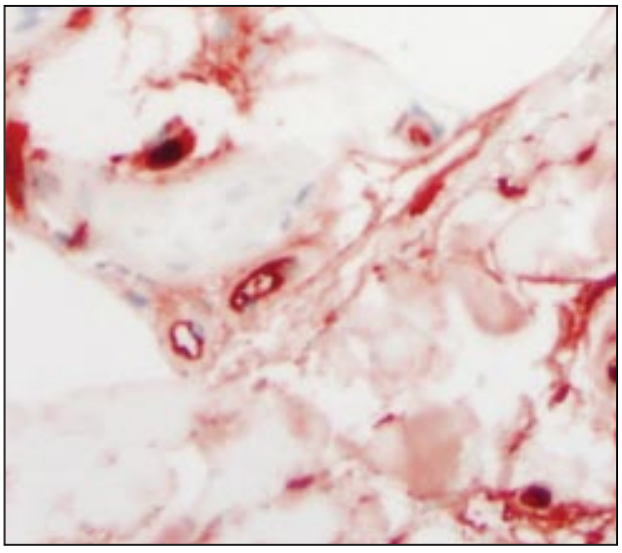

Figure 3. Deep dermal and subcutaneous vessels demonstrating labeling with an anti-IgA immunostudy (original magnification ×200).

flexure and the ileocecal valve. The patient was prescribed a prophylactic regimen of meropenem and metronidazole for colitis, though no precise etiology was identified. An anti-IgA immunostudy was performed on paraffin sections of the original skin biopsy and showed strong labeling in the dermal endothelial cells consistent with immunocomplex deposition (Figure 3). The patient was diagnosed with Henoch-Schönlein purpura (HSP) and her rash and abdominal pain improved with prednisone 60 mg daily. Biopsy of a bone marrow specimen showed myelodysplastic changes and a cellular bone marrow with trilineage dyspoiesis and increased blasts.

Ten days after discharge, the patient's cutaneous eruption had greatly improved, with residual macules present on the dorsum of both feet and only faint reticulated erythema and rare purpura across the lower abdomen and lower extremities. She was scheduled for a second stem cell transplant to treat the myelodysplasia.

Comment

HSP is a systemic leukocytoclastic vasculitis involving arterioles and venules most commonly in the skin, glomeruli, and gastrointestinal tract.[1,2] It is common for affected tissues to histologically demonstrate the presence of IgA in vessel walls. Fever and palpable purpura, predominantly on the buttocks and extremities, often are the first signs of HSP and may be accompanied by arthralgia, abdominal pain, and renal disease.[2] The arthritis can be characterized as transient and oligoarticular, commonly affecting large joints and often with pain out of proportion to objective evidence of synovitis.[2] Signs of peritoneal inflammation may occur and melena is common; more severe gastrointestinal tract complications that may warrant surgical intervention also have been described.[2,3] Renal pathology in patients with HSP involves a spectrum ranging from mild focal glomerulitis to rapidly proliferative glomerulonephritis accompanied by variable amounts of proteinuria and hematuria.[2] In 1990, the American College of Rheumatology identified 4 criteria for separating HSP cases from controls: (1) age 20 years or younger at disease onset, (2) palpable purpura, (3) acute abdominal pain, and (4) biopsy showing granulocytes in the walls of small arterioles or venules. When 2 or more of any of these criteria were present, HSP was distinguished from other forms of vasculitis with a sensitivity of 87.1% and a specificity of 87.7%.[2]

HSP is the most common systemic vasculitis of childhood and has been historically and predominantly viewed as a pediatric disease. HSP is believed to affect adults less frequently but has been reported to be responsible for a substantial percentage of all cases of cutaneous vasculitis among adults.[4] In a retrospective study of patients with HSP, Blanco et al[5] found that HSP represents a more severe

Reported Cases of Henoch-Schönlein Purpura Associated With Malignancy

Malignancy	Age, y	Sex	Author(s), Year Reported
Lymphoma			
Essential thrombocythemia	34	M	Pertuiset et al,[6] 2000
Hodgkin lymphoma	39	M	Ng et al,[13] 1988
Hodgkin lymphoma	29	M	Blanco et al,[14] 1999
Myelodysplasia	43	M	Blanco et al,[15] 1997
Myelodysplasia	57	F	Present case
Non-Hodgkin lymphoma	63	M	Vesole,[16] 1987
Non-Hodgkin lymphoma	68	M	Pertuiset et al,[6] 2000
Non-Hodgkin lymphoma	66	M	Day et al,[17] 2001
Hematologic Malignancy			
Multiple myeloma	50	M	Birchmore et al,[18] 1996
Multiple myeloma	41	M	Conte et al,[19] 2000
Multiple myeloma	50	M	Zickerman et al,[20] 2000
Multiple myeloma	72	M	Arrizabalaga et al,[21] 2003
Multiple myeloma	57	M	Van Der Helm-Van Mil et al,[22] 2003
Solid Tumor			
Anal	46	F	Zurada et al,[23] 2006
Breast	58	M	Hughes et al,[24] 1993
Bronchus	63	M	Cairns et al,[25] 1978
Bronchus	73	M	Cairns et al,[25] 1978
Bronchus	59	M	Maurice,[26] 1978
Bronchus	57	M	Mitchell and Hoffbrand,[27] 1979
Bronchus	79	M	Pfitzenmeyer et al,[28] 1989
Bronchus	78	M	Gutierrez Macias et al,[29] 1992
Bronchus	67	M	Blanco et al,[30] 1997
Bronchus	75	M	Ponge et al,[31] 1998
Kidney	46	F	Pertuiset et al,[6] 2000
Kidney	71	M	Zurada et al,[23] 2006

Malignancy	Age, y	Sex	Author(s), Year Reported
Prostate	60	M	Garcias and Herr,[32] 1982
Prostate	77	M	Pertuiset et al,[6] 2000
Prostate	86	M	Couzi et al,[33] 2002
Prostate	71	M	Zurada et al,[23] 2006
Prostate	80	M	Zurada et al,[23] 2006
Schwannoma	55	M	Fain,[34] 2002
Small bowel	55	M	Hayem et al,[35] 1997
Stomach	67	M	Li Voon Chong and Buckley,[36] 1997

Abbreviations: M, male; F, female.

clinical syndrome in adulthood than in childhood, but the prognosis of patients is equally good in both adult and pediatric populations. An exact cause of HSP has not been identified; however, many processes have been implicated in its development, including infections; drugs; and allergic, rheumatologic, and neoplastic diseases.

Neoplasia in adults with systemic or cutaneous vasculitis has an estimated prevalence of 2.5% to 5.0%, with hematopoietic malignancies occurring more commonly than solid tumors.[6] Although malignancy has been reported to occur in association with nearly all forms of vasculitis, the association between cutaneous hypersensitivity vasculitis and hematopoietic malignancies is most notable.[7] In 1996, Fortin[8] outlined several classic hypotheses explaining the role of neoplastic disease in the development of vasculitic syndromes such as HSP, including the impaired clearance of normally deposited immune complexes, abnormal production of immunoglobulins that may either directly react to vascular antigens and cause in situ immune complex formation or form circulating immune complexes that can then deposit in vessel walls, and common antigens presenting on the surface of malignant cells that may stimulate T-cell activation or the production of immunoglobulin directed not only toward malignant cells but healthy epithelium as well.

The association of vasculitis with malignancy has been reviewed extensively in the literature.[9-12] Sanchez-Guerrero et al[9] found that 11 of 222 patients with vasculitis had associated neoplasia, with both hematologic and solid tumors implicated. Importantly, the authors noted that in 4 of 11 patients with paraneoplastic vasculitis, symptoms of vascular inflammation were evidence of the initial presentation of neoplasia or its recurrence.[9] Kurzrock et al[10] reviewed the manifestation of vasculitis in patients with solid tumors and found that in 71% of cases (25/35), symptoms of vasculitis appeared before or concurrent with the initial recognition or relapse of the tumor. Greer et al[11] described 13 patients with both vasculitis and lymphoproliferative or myeloproliferative syndromes and reported a statistically significant ($P<.0000001$) association between the 2 when compared with all other tumors. The authors further asserted that tumor-associated vasculitis is a heterogeneous group of syndromes that share clinical features; malignancy or its recurrence should be considered in patients with unexplained vasculitis; and although treatment of the underlying neoplasm may lead to resolution of vasculitis, specific therapy for vascular inflammation often is not effective.[11]

HSP specifically has been described in patients with malignancy and vasculitis (Table).[6,13-36] In 2000, Pertuiset et al[6] reviewed 14 cases of adult HSP and found malignant neoplasm in 4 cases. They also identified 15 reports of adult HSP with malignant disease in the literature. Collectively, these 19 cases were compared with 158 adults who had HSP but no malignancy. The authors reported that 63% (12/19) of neoplasms associated with adult HSP were solid tumors, while the remaining 37% (7/19) were hematologic malignancies. Patients with paraneoplastic HSP were older, more likely to be male,

more frequently had joint involvement, and had a lower frequency of prior infection compared with patients with HSP not associated with malignancy. There was no reported statistically significant difference in percentage of patients with cutaneous purpura, gastrointestinal tract involvement, renal involvement, or polyclonal IgA increase between the 2 groups.[6]

More recently, Zurada et al[23] presented the cases of 3 adults who developed HSP within months of diagnosis of a solid tumor or metastasis of a previously diagnosed malignancy. In their review of the world literature, the authors found that 31 cases of malignancy-associated HSP had been reported, and in most cases, the patients were male (94%; 29/31), presented with solid tumors (61%; 19/31), and developed HSP within one month of cancer diagnosis or detection of metastases (55%; 17/31).[23]

The occurrence of vasculitis and malignant disease in the same patient often is difficult to interpret because some patients may exhibit both diseases independently and by chance, while others may have vasculitis as a paraneoplastic syndrome.[6] Currently, the principal sources of data on the association between HSP and malignancy are anecdotal case reports, which can be difficult to use to determine causality and relationship with significance. However, because of the relative rarity of paraneoplastic vasculitis, large studies are difficult, making case reports and smaller literature reviews of unusual presentations valuable.[8]

Conclusion

In summary, we present a 57-year-old woman with a history of follicular lymphoma who developed HSP likely associated with myelodysplastic syndrome. This case is clinically significant because the patient was thought to be in remission of her hematologic disease until her skin findings prompted further evaluation. Her diagnosis of HSP was based on clinical presentation with palpable purpura and abdominal pain, and was confirmed with biopsy and immunohistochemical analyses of purpuric papules that demonstrated leukocytoclastic vasculitis and strong anti-IgA labeling in the dermal endothelial cells consistent with immunocomplex deposition. The patient was placed on a corticosteroid taper and scheduled for stem cell transplantation, with marked improvement demonstrated clinically at her most recent visit.

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