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Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 30-2002. An eight-year-old girl with fever, hemoptysis, and pulmonary consolidations

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Case Records of the Massachusetts General Hospital



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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Case 30-2002

PRESENTATION OF CASE

An eight-year-old girl was admitted to the hospital because of fever, cough, hemoptysis, and pulmonary consolidations.

She had been well until six days before admission, when she was visiting El Salvador. A sore throat developed, with mild fever, a dry cough, and anorexia, and she began to vomit once daily. Three days before admission, she traveled by air to Boston, where she lived, and dyspnea developed. The next day, she began to cough up bright red blood and had right-sided otalgia and a sore throat; the low-grade fever persisted. The hemoptysis and dyspnea worsened, and she was taken to another hospital, where chest radiographs showed pulmonary consolidations. Single doses of ceftriaxone and azithromycin were given, and the following day she was transferred to this hospital.

The girl was an only child. Her immunizations were up to date, and she had received varicella and viral hepatitis A vaccines one month before admission. She had had no known exposure to animals, and she had never been admitted to a hospital. A blood count and the level of lead in the blood at two years of age were reported to be satisfactory. When she was three years old, she was treated for urinary tract infections on two occasions, and urine cultures yielded *Escherichia coli*. A rash, described as erythema multiforme by a physician, had appeared on two occasions, most recently 13 months before admission, but had not been confirmed by biopsy. A tuberculin test 12 months before admission was negative, and she had had no known exposure to tuberculosis. The results of laboratory

studies performed nine months before admission are shown in Table 1.

During the eight months before admission, the girl had had an intermittent papular rash that involved her arms and legs and that had been called a "heat rash" by a physician; it disappeared for a month and then recurred at about the time of her current illness. Five months before admission, the results of a voiding cystourethrographic study performed to evaluate recurrent, painless hematuria were normal, and a renal ultrasonographic examination showed no abnormalities; the symptom was believed to be benign. There was no history of asthma, drug allergy, long-term use of medications, weight loss, or hematochezia. There was no family history of renal disease, cystic fibrosis, or autoimmune disease.

The temperature was 38.3°C, the pulse was 142, and the respirations were 33. The blood pressure was

TABLE 1. HEMATOLOGIC AND BLOOD CHEMICAL DATA.*

VARIABLE	9 MONTHS BEFORE ADMISSION	ON ADMISSION	2ND HOSPITAL DAY
Hematocrit (%)	33.2	23.2	22.0
Erythrocyte sedimentation rate (mm/hr)	32	119	
White cells (per mm ³)		6,500	6700
Differential count (%)			
Neutrophils		66	58
Lymphocytes		29	35
Monocytes		4	4
Eosinophils		1	3
Platelets (per mm ³)		410,000	
Reticulocyte count (%)		1.4	
Mean corpuscular volume (μm ³)	80.2	79	
Prothrombin time (sec)		14.6†	
Partial-thromboplastin time (sec)		Normal	
Glucose (mg/dl)		117	
Phosphorus (mg/dl)		3.4	
Protein (g/dl)		6.8	
Albumin		2.9	
Globulin		3.9	
Urea nitrogen (mg/dl)		4	
Creatinine (mg/dl)		0.4	

*To convert the value for glucose to millimoles per liter, multiply by 0.05551. To convert the value for phosphorus to millimoles per liter, multiply by 0.3229. To convert the value for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the value for creatinine to micromoles per liter, multiply by 88.4.

†The normal range is 11.1 to 13.1 seconds.

110/60 mm Hg. The body weight was 37.3 kg (97th percentile) and the height 127 cm (45th percentile). The oxygen saturation was 95 percent while the patient was breathing oxygen by mask at a rate of 4 liters per minute.

On physical examination, the girl was pale and panting and appeared acutely ill. A maculopapular rash consisted of about 40 scattered lesions that were brown, ovoid, and minimally elevated; for the most part the rash spared the face, hands, and feet. According to the girl's parents, each lesion had begun as a macule, about 1 mm in diameter, that after several days had become a nonblanching papule, 2 to 4 mm in diameter; scabs then developed, without frank ulceration or vesiculation, and the lesions resolved. In addition, there was a circle, about 1 cm in diameter, of small vesicles, each 1 to 2 mm in diameter, on the medial aspect of the left thigh. No petechiae, telangiectases, or oropharyngeal lesions were found, and there was no lymphadenopathy. There were decreased breath sounds over the right upper lobe, with bronchophony; no crackles or intercostal retractions were detected. The heart sounds and the abdomen and rectum were normal; a stool specimen was negative for occult blood. No sign of synovitis was evident. Neurologic examination revealed no abnormalities.

The urine was normal except that the sediment contained 5 to 10 white cells and 3 to 5 red cells per low-power field. Laboratory tests were performed (Table 1). The levels of conjugated and total bilirubin, calcium, magnesium, electrolytes, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase were normal. Analysis of a specimen of arterial blood, obtained while the patient was breathing oxygen by mask at a rate of 5 liters per minute, showed that the partial pressure of oxygen was 178 mm Hg, the partial pressure of carbon dioxide 38 mm Hg, and the pH 7.43.

Chest radiographs (Fig. 1) showed complete opacification of the right upper lobe and confluent opacities in both lower lobes; no pleural effusion was evident, and the heart, mediastinum, and bony structures appeared normal. A computed tomographic (CT) examination of the paranasal sinuses (Fig. 2) revealed mucosal thickening of the left maxillary, right posterior ethmoid, and sphenoid sinuses, without erosion or destruction of bone; the frontal sinuses were not yet pneumatized, and there was scattered opacification of the mastoid air cells. The orbits appeared normal; there was slight prominence of the adenoids, which was within normal limits for the patient's age. CT scanning of the chest (Fig. 3), performed after the intravenous administration of contrast material, disclosed nearly complete consolidation in the right upper lobe, with air bronchograms. Confluent, nodular opacities and patchy, ground-glass opacities were scat-



Figure 1. Radiograph of the Chest Showing Nearly Complete Collapse of the Right Upper Lobe.

There are confluent opacities in both lower lobes.

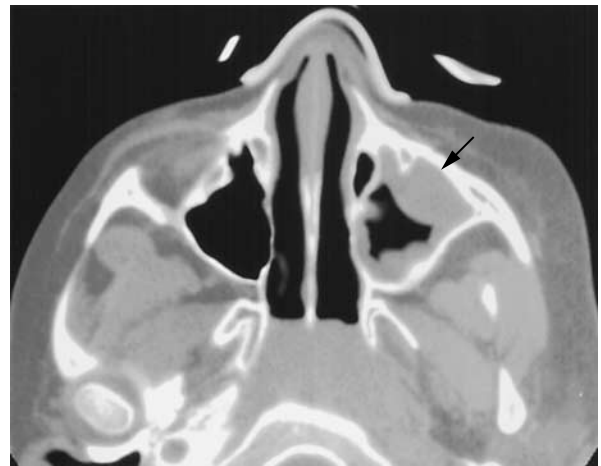


Figure 2. CT Scan of the Paranasal Sinuses Showing Mucosal Thickening in the Left Maxillary Sinus (Arrow).

tered throughout both lower lobes, with air bronchograms in some areas. No cavitation, pleural effusion, or lymphadenopathy was detected. The major airways, heart, great vessels, and bones appeared normal, as did the areas of the upper abdomen that were visible on the scans.

A consultant in pediatric otolaryngology found pus in the right middle ear and a serous effusion in the

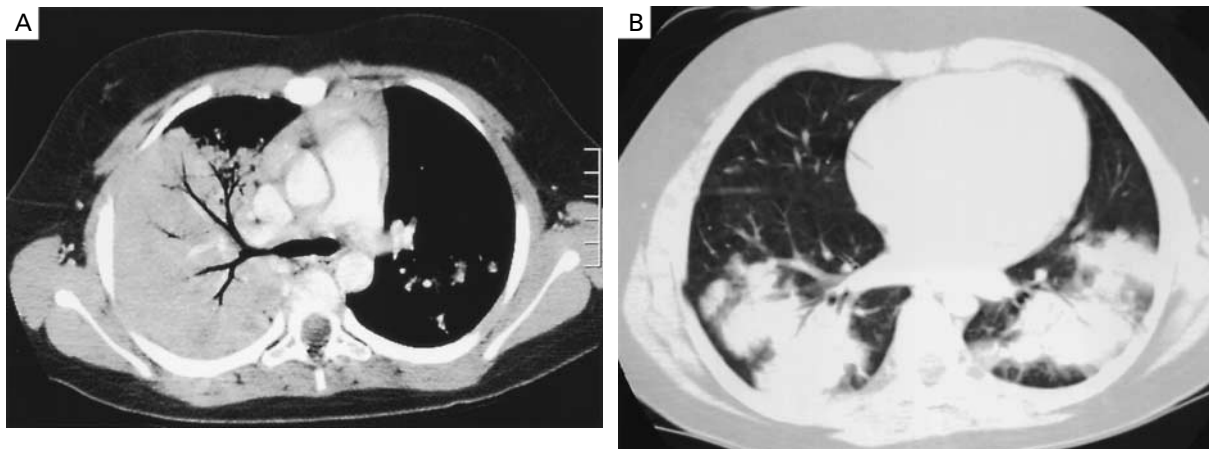


Figure 3. CT Scan of the Chest Obtained after the Administration of Contrast Material.

The image with soft-tissue windows (Panel A) shows complete consolidation in the posterior segment of the right upper lobe and nearly complete consolidation in the anterior segment of that lobe. The consolidated area outlines an air bronchogram. The image with lung windows (Panel B) shows patchy areas of ground-glass opacity in both lower lobes.

left. There was purulent drainage from both maxillary sinuses. Shallow excoriations were seen along the anterior part of the nasal septum. No ulcerated lesions were detected on the turbinates. The pharynx and tonsillar pillars were erythematous. Shotty posterior lymph nodes were palpated bilaterally. The larynx appeared normal.

Therapy with ceftriaxone and azithromycin was continued, and vancomycin and acetaminophen were added to the regimen. On the evening of admission, the temperature rose to 38.9°C. The hemoptysis persisted, although the patient never coughed up sputum. On the second hospital day, the temperature rose to 38.1°C, and the respiratory rate ranged between 30 and 56 breaths per minute. Another specimen of urine, examined by a nephrologist, contained no protein or white cells, but there were many red cells, some of which were dysmorphic, and one red-cell cast. The results of laboratory tests are shown in Table 1. Preliminary examination of a blood culture, a urine culture, and a throat culture revealed no organisms, and a test for legionella urinary antigen was negative. The findings on two sets of chest radiographs remained unchanged. A bronchoscopic examination confirmed the presence of blood in the bronchial tree and did not reveal an obvious source. An aspirated specimen of sputum (the only sputum that could be obtained during the girl's hospital stay) contained a very small number of epithelial cells, no neutrophils, and abundant gram-negative rods; no fungi or acid-fast bacilli were seen. Culture findings and the results of additional laboratory tests were pending.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

DR. BRIAN P. O'SULLIVAN*: May we review the radiographic findings?

DR. DIEGO JARAMILLO (Radiology): The initial radiograph of the chest shows evidence of consolidation, predominantly in the right upper lobe, as well as patchy areas of consolidation in the left lung and the right lower lobe (Fig. 1). A lateral view confirmed the predominance of the consolidation in the right upper lobe. A CT scan of the sinuses (Fig. 2) shows evidence of thickening of the mucosa of the left maxillary and sphenoid sinuses.

A CT scan of the chest obtained after the intravenous administration of contrast material again shows marked consolidation and air bronchograms in the right upper lobe (Fig. 3A). A CT scan with lung windows shows bilateral areas of ground-glass opacities in addition to confluent, patchy opacities (Fig. 3B). There is normal enhancement of the pulmonary arteries, without evidence of necrosis.

DR. O'SULLIVAN: The most important aspects of the child's history and presentation are her chronic renal problems and acute pulmonary hemorrhage. This constellation of findings places the illness in the category of pulmonary–renal syndromes.^{1,2} Primary pulmonary–renal syndromes include Goodpasture's syndrome, systemic lupus erythematosus, and small-vessel vasculitides (Table 2).^{1,2} The chronic and re-

*Director of the Cystic Fibrosis Center, the Pediatric Pulmonary, Asthma, and Cystic Fibrosis Center, UMass Memorial Health Care; associate professor of pediatrics, University of Massachusetts Medical School — both in Worcester.

TABLE 2. COMPARATIVE FEATURES OF THE PULMONARY-RENAL SYNDROMES.*

FEATURE	GOODPASTURE'S SYNDROME	SYSTEMIC LUPUS ERYTHEMATOSUS	WEGENER'S GRANULOMATOSIS	MICROSCOPIC POLYANGIITIS
Pulmonary hemorrhage	++++	+ to ++	+++	+++
Glomerulonephritis†	++++	+++ to +++++	++++	++++
Upper-airway involvement	0	+ to ++	++++	++
Rash	0 to +	++++	+++	+++
Arthralgias	0	++++	+++	+++
Markedly elevated erythrocyte sedimentation rate	0 to +	++++	++++	++++
Serologic findings	Anti-glomerular basement membrane antibody; very rarely, ANCA	Antinuclear antibody; anti-double-stranded DNA antibody; rarely, p-ANCA	c-ANCA; rarely, p-ANCA	p-ANCA; c-ANCA

*0 denotes not found, + very rare, ++ uncommon, +++ common, and +++++ usually present; ANCA denotes antineutrophil cytoplasmic antibody (p-ANCA with a perinuclear pattern of staining and c-ANCA with a cytoplasmic pattern of staining).

†Glomerulonephritis is defined as hematuria or the presence of red cells or red-cell casts in the urine, with or without proteinuria.

current skin findings and the problems affecting the paranasal sinuses and ears are also striking. The slightly elevated erythrocyte sedimentation rate nine months before admission and the abnormal urinary sediment five months before admission are evidence of long-standing, rather than acute, disease.

Goodpasture's Syndrome

Goodpasture's syndrome is characterized by pulmonary hemorrhage and glomerulonephritis in patients with circulating antibodies against glomerular basement membrane or with linear immunofluorescent staining of IgG in the basement membranes of pulmonary or renal tissue.³⁻⁵ Although the syndrome is unusual in childhood, cases in children have been reported, including two in girls, 13 and 17 years old, who were the subjects of discussion at these conferences in 1993.^{6,7} In Goodpasture's syndrome, unlike other immune-complex diseases, such as systemic lupus erythematosus, there is little generalized inflammation, and a strikingly elevated erythrocyte sedimentation rate is uncommon.⁵ The skin and upper respiratory tract are generally not involved. The prominent involvement of the skin, ears, and sinuses in this child, together with the markedly elevated erythrocyte sedimentation rate, strongly argues against a diagnosis of Goodpasture's syndrome.

Systemic Lupus Erythematosus

Systemic lupus erythematosus has been well documented in children, especially young girls, and is commonly associated with rashes. Twenty percent of persons with systemic lupus erythematosus present between the ages of 8 and 16 years.⁸ This diagnosis should be considered in a child who has an elevated

erythrocyte sedimentation rate, abnormal results on urinalysis, and arthralgias or arthritis.

Up to 50 percent of patients with systemic lupus erythematosus have involvement of the respiratory tract at some time during their illness.⁸ Diffuse alveolar hemorrhage has been well described, with at least 72 such cases reported in the literature by 1997,⁹ including cases reported in children.¹⁰ Alveolar hemorrhage may occur abruptly and may be the first manifestation of systemic lupus erythematosus; however, most patients with hemorrhage have already received the diagnosis.

The cutaneous findings in systemic lupus erythematosus are most prominent in sun-exposed areas of the skin. The malar butterfly rash, which occurs in only about a third of patients, is a well-recognized manifestation of the disease.¹¹ Polymorphous rashes on other parts of the body, including macular and papular eruptions, urticaria, petechiae, and purpuric lesions, are common. Erythema multiforme in association with systemic lupus erythematosus, known as Rowell's syndrome, has been described in a few patients and often involves the presence of chilblains in addition to erythema multiforme.¹² Unlike this patient, most patients with Rowell's syndrome are photosensitive. Otolaryngologic manifestations are uncommon in patients with systemic lupus erythematosus. Recurrent noninfectious pharyngitis and oral ulcers are seen, but chronic problems of the ears and sinuses are not.¹¹ Finally, the diagnosis of systemic lupus erythematosus is difficult to make in the absence of a positive antinuclear-antibody test and in the absence of a positive test for antibodies against double-stranded DNA.

In the case under discussion, the underlying nephritis, the polymorphous rash and history of erythe-

ma multiforme, and the markedly elevated erythrocyte sedimentation rate are all consistent with a diagnosis of systemic lupus erythematosus. However, because the patient has no photosensitivity, no arthralgias, less severe renal dysfunction than would be expected in a person with systemic lupus erythematosus, and a rash that is atypical of the disease, systemic lupus erythematosus is an unlikely diagnosis.

Small-Vessel Vasculitides

The final group of diseases associated with pulmonary–renal syndromes are the small-vessel vasculitides. These include Wegener’s granulomatosis, microscopic polyangiitis, the Churg–Strauss syndrome, Henoch–Schönlein purpura, and cryoglobulinemia.¹³ This child’s clinical picture does not fit either Henoch–Schönlein purpura or cryoglobulinemia. The Churg–Strauss syndrome can cause the findings described in this case; however, the absence of peripheral-blood eosinophilia and of a history of asthma essentially rules out this diagnosis.

Both Wegener’s granulomatosis and microscopic polyangiitis are pauci-immune vasculitides that involve the medium and small arteries, arterioles, and venules and capillaries¹⁴ and that do not involve substantial deposition of immune complexes in the tissue. The presence of granulomas in Wegener’s granulomatosis distinguishes it from microscopic polyangiitis, and the expression of antineutrophil cytoplasmic antibodies (ANCA) differs in the two diseases. The clinical presentation of patients with these diseases, however, can be indistinguishable. In fact, cases have been reported in which patients who initially presented with microscopic polyangiitis without granulomas subsequently had granulomatous lesions and thus were later considered to have Wegener’s granulomatosis.¹⁵

Wegener’s Granulomatosis

Criteria for the diagnosis of Wegener’s granulomatosis include nasal or oral inflammation, abnormal findings on chest radiographs, abnormal urinary sediment, and granulomatous inflammation within an arterial wall or in a perivascular distribution.¹⁶ The upper respiratory problems associated with Wegener’s granulomatosis include rhinorrhea, nasal mucosal ulceration or crusting, serous otitis media, and sinus pain or drainage.¹⁷

Pulmonary disease develops in nearly three quarters of children with Wegener’s granulomatosis, and cutaneous manifestations develop in approximately half at some point in the course of their illness.¹⁸ Cutaneous lesions, which may precede other systemic manifestations by a period of months, occur most commonly on the legs. The predominant skin lesion in small-vessel vasculitis syndromes is palpable pur-

pura. Other lesions may be vesicular, papular, or nodular, and urticaria may be seen.¹⁹ Renal manifestations, including proteinuria and the presence of red cells and red-cell casts in the urine, are seen in 60 to 80 percent of patients with Wegener’s granulomatosis.^{20–22} At the time of presentation, the renal involvement is usually asymptomatic, but even in such cases, glomerulonephritis can progress rapidly.

Findings on radiographs of the chest and on CT scans are nonspecific. Air-space filling and the presence of air bronchograms are seen in cases of acute pulmonary hemorrhage. If diffuse alveolar hemorrhage is absent, radiographic findings of multiple nodules or cavitary lesions suggest a diagnosis of Wegener’s granulomatosis. In a cohort of 23 children, 10 (43 percent) had chest films that showed nodules.¹⁸

Microscopic Polyangiitis

The clinical manifestations of microscopic polyangiitis include glomerulonephritis, weight loss, vasculitic rash, fever, arthralgias, mononeuritis multiplex, and pulmonary disease (including pulmonary hemorrhage).²² Both the upper and lower airways may be involved. Ear and sinus involvement is much less common in microscopic polyangiitis than it is in Wegener’s granulomatosis.^{15,22}

Diagnostic Tests for Small-Vessel Vasculitides

Tissue Biopsy

A diagnosis of Wegener’s granulomatosis or microscopic polyangiitis can be made when characteristic histologic abnormalities are identified in a patient with clinically compatible findings. The histologic changes may be patchy; thus, the likelihood that examination of a biopsy specimen will show diagnostic abnormalities depends on the site of the biopsy, the level of activity of the disease, and the amount of tissue obtained. Table 3 outlines the advantages and disadvantages of biopsies at various sites in patients with pulmonary–renal syndromes. Biopsy of the upper airway (i.e., nose or sinus) is diagnostic of Wegener’s granulomatosis in only about 20 percent of cases.²¹ Open lung biopsy is the procedure most likely to be diagnostic, but it is associated with increased mortality rates among patients with vasculitis.²³ Transbronchial biopsy is safer but not as reliable.²¹ A biopsy of any tissue that shows changes typical of Wegener’s granulomatosis or microscopic polyangiitis is diagnostic, even if the yield is low.

Antinuclear Cytoplasmic Antibodies

I expect that this child’s serum was analyzed for ANCA. These antibodies occur in two forms, one with a cytoplasmic pattern of staining (c-ANCA) and one with a perinuclear pattern of staining (p-ANCA).²⁴ The target antigen of c-ANCA is pro-

teinase 3; p-ANCA is usually directed against myeloperoxidase but may interact with other antigens (Table 4). The results of ANCA testing are one of the few ways in which Wegener's granulomatosis and microscopic polyangiitis differ.

ANCA directed against proteinase 3 (c-ANCA) is found in 70 to 90 percent of patients with active Wegener's granulomatosis.^{21,25} The positive predictive value of any test depends on the pretest probability of the presence of the disease. Thus, in cases in which the probability of Wegener's granulomatosis is low, a positive test for c-ANCA should be interpreted cautiously; however, in a case such as the one under dis-

ussion, in which the likelihood of Wegener's granulomatosis is very high on clinical grounds, a positive c-ANCA test could be considered diagnostic, with a positive predictive value above 99 percent. Falk and Jennette²⁵ have stated that the specificity of c-ANCA is so high that in the appropriate clinical circumstances, patients should be treated for Wegener's granulomatosis on the basis of a positive test.

ANCA directed against myeloperoxidase (p-ANCA) is seen in microscopic polyangiitis much more often than it is in Wegener's granulomatosis²⁶; in two studies, p-ANCA was detected in 56 to 87 percent of patients with microscopic polyangiitis.^{15,27} In contrast,

TABLE 3. ADVANTAGES AND DISADVANTAGES OF OBTAINING TISSUE FROM SPECIFIC ORGANS TO DIFFERENTIATE THE PULMONARY-RENAL SYNDROMES.

ORGAN	ADVANTAGES	DISADVANTAGES
Sinus or nose	Tissue is accessible; procedure is safe and simple	Tissue is not involved in all pulmonary-renal syndromes; procedure has poor sensitivity (only 20% positive in known Wegener's granulomatosis)
Skin	Tissue is accessible; procedure is safe and simple	Tissue may not be involved; biopsy may be nonspecific and nondiagnostic
Kidney	Tissue is relatively accessible and is usually involved; procedure provides most reliable information about severity of renal involvement in systemic lupus erythematosus and differentiates Goodpasture's syndrome from other pulmonary-renal syndromes	Procedure is invasive (minimally); it may not differentiate among Wegener's granulomatosis, microscopic polyangiitis, and rapidly progressive glomerulonephritis; sampling error is possible (since it is a blind procedure); even in proved Wegener's granulomatosis, vasculitis and granuloma are uncommon
Lung	Visualization allows acquisition of good specimen; procedure is generally diagnostic; transbronchial biopsy can be performed	Procedure is invasive; transbronchial biopsy is unreliable (because of sampling error); open biopsy increases mortality

TABLE 4. COMPARISON OF TESTS FOR ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES WITH A CYTOPLASMIC PATTERN OF STAINING (c-ANCA) AND A PERINUCLEAR PATTERN OF STAINING (p-ANCA).

p-ANCA	c-ANCA
Antibodies to strong cations	Antibodies to neutral proteins or weak cations (e.g., proteinase 3)
Target antigen is usually myeloperoxidase but nonspecific antigenic interactions may occur	Target antigen is proteinase 3
Most often positive in patients with microscopic polyangiitis or pauci-immune, rapidly progressive glomerulonephritis	Highly specific for Wegener's granulomatosis
Positive in approximately 50% of patients with microscopic polyangiitis	Positive in 70-90% of patients with Wegener's granulomatosis
Positive in 5-30% of patients with Wegener's granulomatosis	Occasionally positive in patients with microscopic polyangiitis or the Churg-Strauss syndrome (15-25%)
May be positive in patients with systemic lupus erythematosus, Goodpasture's syndrome, inflammatory bowel disease, or rheumatoid arthritis	Very rarely positive in patients with certain infectious diseases (e.g., amoebiasis)

5 to 30 percent of patients with Wegener's granulomatosis have positive tests for p-ANCA. Since lesions of Wegener's granulomatosis (such as microscopic granulomas and fleckmilz⁶) may not be evident until postmortem examinations are performed, it may be impossible to differentiate Wegener's granulomatosis from microscopic polyangiitis during life. Niles et al.²⁸ proposed the term "ANCA-associated lung hemorrhage and nephritis" to cover this spectrum of disease.

Summary

In summary, this patient had a pulmonary–renal syndrome, and the probable diagnosis is Wegener's granulomatosis or microscopic polyangiitis. I think the diagnostic procedure consisted of serologic tests for anti–glomerular basement membrane antibodies, antinuclear antibodies, anti–double-stranded DNA antibodies, and ANCA (with specific testing for antibodies directed against proteinase 3 and myeloperoxidase) and that the test for ANCA was positive.

DR. ROBERT B. COLVIN (Pathology): Dr. Anselmo, what were your clinical impressions?

DR. MARK A. ANSELMO (Pulmonary Medicine): This acutely ill child had evidence of pulmonary hemorrhage, and we initially believed that she had necrotizing pneumonia with hemorrhage, for which she was treated appropriately. Our subsequent diagnosis was a vasculitis, and the leading possibilities were Wegener's granulomatosis and microscopic polyangiitis. Because we thought her condition was stable, we opted to treat the pneumonia and wait for the results of the serologic tests.

CLINICAL DIAGNOSES

Necrotizing pneumonia with hemorrhage.
? Vasculitis (Wegener's granulomatosis or microscopic polyangiitis).

DR. BRIAN P. O'SULLIVAN'S DIAGNOSIS

ANCA-associated pulmonary hemorrhage and nephritis (Wegener's granulomatosis or microscopic polyangiitis).

PATHOLOGICAL DISCUSSION

DR. JOHN L. NILES (Pathology): The diagnostic study was a serologic test for ANCA by indirect immunofluorescence, which was positive, with a p-ANCA pattern; an enzyme-linked immunosorbent assay confirmed the presence of antibodies to myeloperoxidase; the antibody titer was 46 U. (A value of 2.8 U or higher is considered a positive result.) An enzyme-linked immunosorbent assay for antibodies to proteinase 3 was negative. The pattern of ANCA staining — cytoplasmic versus perinuclear — is suggestive of but not specific for the particular type of antibody. Although the c-ANCA pattern is a reliable marker

of the presence of anti–proteinase 3 antibodies, the p-ANCA pattern is not specific for the presence of antimyeloperoxidase antibodies. Thus, "anti–proteinase 3 ANCA" and "antimyeloperoxidase ANCA" are more specific terms than "c-ANCA" and "p-ANCA." The presence of antibodies to myeloperoxidase or proteinase 3 may be virtually diagnostic (in the appropriate clinical setting) of Wegener's granulomatosis, microscopic polyangiitis, or a related form of vasculitis.

Patients who have antimyeloperoxidase antibodies typically do not have granulomas, and patients who have granulomatous lesions more often have anti–proteinase 3 antibodies than antimyeloperoxidase antibodies.

DR. LORI A. ERICKSON (Pathology): A biopsy specimen of the skin of the left upper thigh was obtained. Microscopical examination showed necrotizing vasculitis involving the small vessels (capillaries, venules, and arterioles) of the dermis. There was extravasation of red cells and an interstitial infiltrate composed predominantly of polymorphonuclear neutrophils, with karyorrhexis (Fig. 4). Granulomas and tissue eosinophilia were not identified. The histologic reaction pattern was that of a small-vessel vasculitis.

Small-vessel vasculitis involves vessels smaller than arteries, including capillaries, venules, and arterioles.²⁹ Arteries may also be involved. In contrast, medium-vessel vasculitis involves arteries but does not involve small vessels. If, on histologic examination, only arteritis is identified, it may be impossible to differentiate between small-vessel and medium-vessel vasculitis. The distinction is important, however, since the associated clinical syndromes are different. The medium-vessel vasculitides include polyarteritis nodosa and, in children, Kawasaki's disease. The differential diagnosis of small-vessel vasculitis is broad, and clinical and laboratory data are necessary to establish a specific diagnosis. In this case, a biopsy specimen of the maxillary sinus mucosa was obtained; it showed only nonspecific chronic inflammation, without vasculitis or granulomas. Additional tests showed no evidence of serum antinuclear antibodies or of antibodies to Goodpasture's antigen. Because of the positive result on ANCA testing, the histologic differential diagnosis was narrowed to the ANCA-associated small-vessel vasculitides. The histologic findings in the skin specimen, in conjunction with the clinical information and the presence of antimyeloperoxidase antibodies, support the diagnosis of microscopic polyangiitis.

DR. J. PATRICK WHELAN (Pediatric Rheumatology): I saw this patient in the hospital and have followed her since she was discharged. A number of studies have demonstrated the benefit of cyclophosphamide in the context of ANCA-associated vasculitis.²² In this case, methylprednisolone and cyclophosphamide were

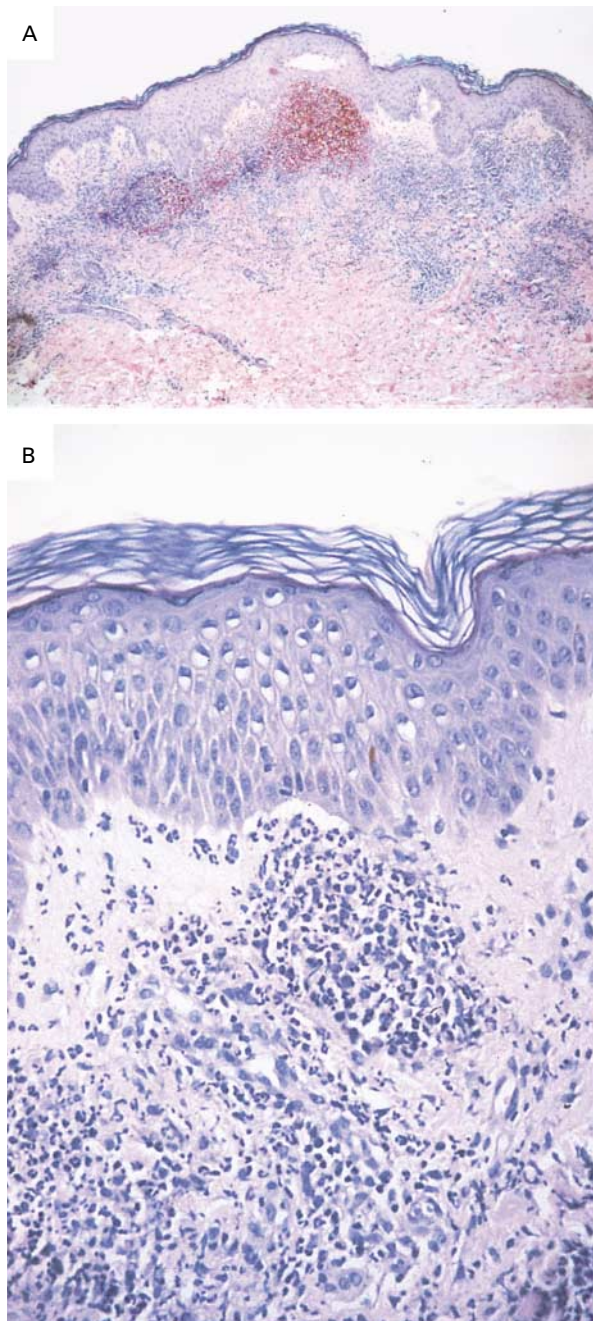


Figure 4. Biopsy Specimen of the Skin (Hematoxylin and Eosin).

A low-power view shows extravasation of red cells and a dense inflammatory infiltrate (Panel A, $\times 80$). Neutrophils surround and infiltrate small blood vessels (Panel B, $\times 250$).

administered daily, along with trimethoprim–sulfamethoxazole three times per week for prophylaxis against *Pneumocystis carinii* pneumonia.

The disease quickly went into remission, although the patient had transient leukopenia during the third month of treatment and a marked weight gain while taking high-dose prednisone. The dose of corticosteroids was tapered at six weeks to an every-other-day regimen as recommended in a recent study of children and adults with Wegener's granulomatosis.³⁰

DR. COLVIN: Did her p-ANCA disappear after treatment?

DR. WHELAN: Repeated testing after nine months of remission showed an increase in the antityloperoxidase-antibody titer, from 46 to 84 U. There has been some controversy about whether ANCA-associated antibody titers can predict the recurrence of disease.

DR. COLVIN: Dr. Niles, what is the value of ANCA testing for monitoring?

DR. NILES: There is some correlation between the ANCA titers and disease activity. A rapidly rising ANCA titer during remission indicates an increased probability of flaring of disease; a rapidly falling or negative ANCA titer during remission points to a decreased probability of early relapse. For patients with rising titers, frequent follow-up evaluations to watch for breakthrough of disease appear to be appropriate, and increasing or decreasing therapy on the basis of ANCA titers may be warranted.

A PHYSICIAN: Did the cutaneous lesions resolve in this case?

DR. WHELAN: Because of the history of recent varicella vaccination, we initially considered the possibility that the patient had a post-vaccination pneumonitis, reported by the manufacturer of the vaccine as a possible adverse effect. However, the skin-biopsy specimen showed no evidence of varicella infection, and the viral cultures were negative. The rash resolved rapidly after the start of treatment with methylprednisolone and cyclophosphamide and has not recurred.

DR. O'SULLIVAN: How long do you expect to continue the cyclophosphamide therapy, and what implications does that have for the girl's reproductive health?

DR. WHELAN: The consensus is that immunosuppressive treatment should be continued for at least one year after the disease has remitted or been brought under control. A staged approach to therapy with cyclophosphamide induction and a switch to another form of cytotoxic therapy after six months has recently been recommended to minimize adverse effects of cyclophosphamide treatment.³⁰ Ovarian function is generally considered to be safe from cyclophosphamide toxicity in the premenarchal period.³¹⁻³³ In this case, six months after the disease remitted, the ther-

apy was changed to azathioprine (1 mg per kilogram of body weight per day), a regimen currently under investigation in a large European trial. Weekly methotrexate has also been recommended as a second-step cytotoxic agent after remission has been achieved with the administration of cyclophosphamide.

ANATOMICAL DIAGNOSIS

Antimyeloperoxidase ANCA-associated vasculitis (microscopic polyangiitis), with pulmonary hemorrhage.

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35-MILLIMETER SLIDES FOR THE CASE RECORDS

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