Diagnostic Usefulness of Nasal Biopsy in Wegener's Granulomatosis

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Wegener's granulomatosis (WG) frequently involves the upper respiratory tract, and nasal mucosal biopsy is often initially used to establish the diagnosis. To evaluate the diagnostic efficacy of nasal biopsy in WG, we reviewed the pathologic features of 30 such biopsy specimens from 17 patients with well-documented WG. Active vasculitis (granulomatous or nongranulomatous) was identified in seven of the patients (41%). The presence of extravascular foci of necrosis in lung biopsy samples has recently received attention as a characteristic feature of WG. Similar foci were found in the nasal samples from six of our patients, although vasculitis was absent in the samples from two of them. If extravascular foci of necrosis are regarded as characteristic or even diagnostic of WG, two additional patients in our series could be regarded as having had diagnostic nasal biopsies (nine of 17 patients). Nasal biopsy could thus be considered as diagnostic in 53% of the patients. Samples larger than 5 mm in greatest dimension were more likely to contain diagnostic features than were smaller samples ($P = 0.002$). HUM PATHOL **22:107–110.**

Wegener's granulomatosis (WG) is a systemic disease which is frequently lethal if untreated. While prompt treatment with immunosuppressive and cytotoxic agents can significantly alter the aggressive course of the disease, potentially severe side effects may result from therapy.[1] In this light, histologic confirmation is usually sought to support the clinical diagnosis of WG before therapy is instituted. The nasal mucosa is often involved in WG and is an easily accessible biopsy site.[2] In this report we describe the pathologic manifestations of nasal mucosal involvement by WG and evaluate the diagnostic value of the nasal biopsy.

MATERIALS AND METHODS

Demographic data, clinical findings, treatment, and outcome were determined from the clinical records of 17 patients treated for WG at the University of Michigan Medical Center, Ann Arbor, MI. Each patient manifested signs and symptoms suggestive of WG and underwent nasal biopsy. Three patients were regarded as having had diagnostic specimens. Either a noninfectious granulomatous vasculitis of the lung (seven patients) or a necrotizing glomerulonephritis (seven patients) was subsequently histologically documented in the remaining 14 patients whose nasal samples were regarded as nondiagnostic. The pathologic findings of the 30 nasal and paranasal sinus biopsy samples obtained from these patients formed the basis of this study.

From two to four routinely stained histologic sections were reviewed for each sample. Silver methenamine and Ziehl Neelsen-stained sections were examined for each case; fungal organisms and acid-fast bacilli were not identified. The elastica of blood vessels was examined with the Movat pentachrome stain. The presence or absence of mucosal ulcers was noted, as were the types of inflammatory cells present in the submucosal stroma. The size of the biopsy sample was recorded and correlated with the presence of vasculitis (granulomatous or nongranulomatous) and with foci of extravascular necrosis (Fisher exact test).

Nongranulomatous vasculitis was defined as the presence of fibrinoid necrosis and transmural inflammatory cells within the walls of blood vessels, primarily venules and arterioles, not located in or adjacent to an ulcer (Fig 1). Enlarged, plump endothelial cells, fibrin thrombi, and extravasated red blood cells were other often-observed features. When associated with a histiocytic infiltrate or multinucleated giant cells, the findings were considered indicative of granulomatous vasculitis[3,4] (Fig 2). Rarely, palisades of histiocytes were arranged around these foci. Intimal fibrosis was considered to be evidence of prior vascular injury. Clumped or "granular" collagen comprised microscopic foci of extravascular necrosis (Fig 3). The altered collagen was often more eosinophilic than the adjacent uninvolved collagen. Clusters of neutrophils were often present at these foci (Fig 4).

OBSERVATIONS

Clinical

The ages of the 17 patients ranged from 17 to 77 years (mean, 46 years); 10 of the patients were male. Sixteen patients presented with upper respiratory tract disorder signs or symptoms. None of the patients had a history of asthma or had asthmatic symptoms. The remaining patient initially sought medical attention because of dyspnea and increased sputum production; subsequent occurrence of upper respiratory tract disorder symptoms occasioned biopsy of the nasal mucosa.

Sixteen of the patients were treated with steroids and cytotoxic agents, and one of the patients also received radiation therapy to the nasal lesion. Clinical follow-up intervals ranged from 1 month to 24 years. A single patient was lost to follow-up prior to the

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Key words: Wegener's granulomatosis, nasal biopsy.

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0046-8177/91/2202-0003$5.00/0

FIGURE 1. Nasal septum. Inflammatory cells involve a portion of a venule lined by endothelial cells. Inflammatory cells are scattered about the vessel as well. (Hematoxylin-eosin stain; magnification × 250.)

initiation of therapy. A favorable response or complete remission was noted in 15 patients; one patient died from sepsis during the first month of therapy. The clinical findings are summarized in Table 1.

Pathologic

Biopsy samples obtained from four patients manifested granulomatous vasculitis (five of 30 samples). An additional three patients had evidence of nongranulomatous vasculitis (eight of 30 samples). Vasculitis was absent in the specimens obtained from the remaining 10 patients, although specimens from two of these patients demonstrated foci of extravascular fibrinoid necrosis. Nine biopsy samples obtained from four patients had both foci of extravascular necrosis and either granulomatous (one patient) or nongranulomatous vasculitis (three patients). Four biopsy samples from three other patients manifested granulomatous vasculitis although extravascular foci of fibrinoid necrosis were absent. Intimal fibrosis or fibrous obliteration of blood vessel lumens was noted in nine samples obtained from seven patients.

Variable numbers of plasma cells, lymphocytes, and neutrophils were present in 27 of the samples, while scattered multinucleated giant cells and small numbers of eosinophils were present in 16 and 19 biopsy specimens, respectively. Ulceration of the mucosal surface was noted in 21 specimens. The pathologic features and their incidence are summarized in Table 2.

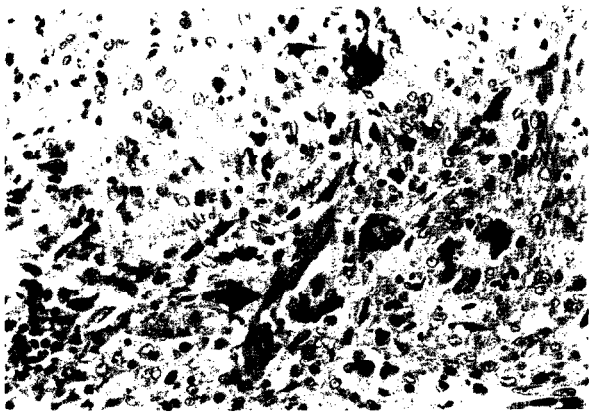

FIGURE 2. Multinucleated giant cells and other inflammatory cells partially destroy this blood vessel which is lined by swollen endothelial cells (arrow). (Hematoxylin-eosin stain; magnification × 250.)

FIGURE 3. Extravascular necrotic focus. Note the granular appearance of the collagen. Most of the nuclei are intact. (Hematoxylin-eosin stain; magnification × 250.)

A sample size larger than 5 mm in at least one dimension was significantly correlated with the presence of an active vasculitis and foci of fibrinoid necrosis ($P = 0.002$). The presence or absence of granulomatous vasculitis did not correlate with sample size; this lack of correlation may have been due to the paucity of samples which manifested this finding (five of 30 specimens).

DISCUSSION

Wegener's granulomatosis was first described by Klinger[5] and subsequently reported in greater detail by Wegener.[6] The marked nasal ulceration and necrosis led Wegener to conclude that the nose was the primary site of the disease which subsequently produced inflammation and necrosis of the lungs and kidneys.[7] Over the ensuing years, however, diagnostic criteria primarily emphasized the necrotizing granulomatous lesions of the lower respiratory tract,

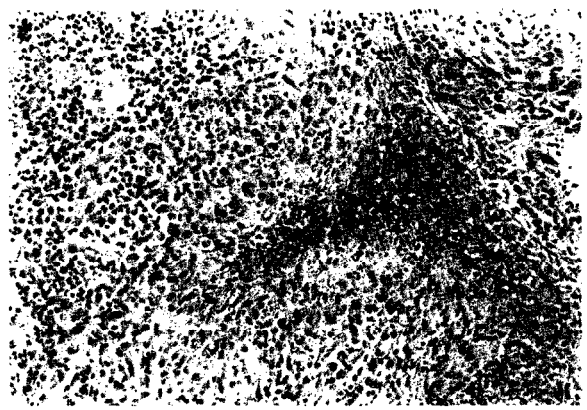

FIGURE 4. Microabscess. Histiocytes surround the main cluster of neutrophils. (Hematoxylin-eosin stain; magnification × 125.)

TABLE 1. Clinical Findings

Patient No.	Age/Sex	Presenting Signs/Symptoms	Therapy
1	32/F	Hemoptysis, sinusitis, shaking chills, diaphoresis	cyclophos/pred
2	48/M	Sinusitis, chest pain, acral cyanosis	cyclophos/pred
3	66/M	Hoarseness, purulent nasal discharge, hemoptysis, hearing loss, weight loss	cyclophos/pred
4	76/M	Sinusitis, headache, otalgia, fever, chills, weakness, weight loss	cyclophos/pred
5	77/F	Sinusitis, rhinorrhea, cough, hemoptysis	cyclophos/pred
6	23/M	Sinusitis, multiple upper respiratory infections, bloody nasal discharge, otalgia, ophthalgia, hematuria	cyclophos/pred
7	30/F	Recurrent epistaxis, sinusitis, proptosis	cyclophos/pred
8	45/M	Nasal congestion, fevers, headache, malaise, otalgia, lung nodules	cyclophos/pred
9	17/M	Epistaxis, nasal ulcers, lung infiltrates	
10	39/M	Nasal congestion and bloody discharge, otalgia, perforated tympanic membrane, weight loss	cyclophos/pred
11	22/F	Saddle nose	cyclophos/pred
12	53/M	Sinusitis, perforated nasal septum, epistaxis	cyclophos/pred
13	57/F	Epistaxis, hemoptysis, cough, malaise, pulmonary infiltrates	cyclophos/pred
14	30/F	Sinusitis, hemoptysis, arthralgia	cyclophos/pred
15	51/M	Epistaxis, retro-orbital pain, weakness	cyclophos/pred, radiation therapy
16	56/F	Maxillary sinus pain, left sinus congestion	cyclophos/pred
17	67/M	Sputum production, shortness of breath	cyclophos/pred

Abbreviations: cyclophos, cyclophosphamide; pred, prednisone.

and the presence of a generalized necrotizing vasculitis and glomerulonephritis.[8,9] Carrington and Liebow later drew attention to a subset of patients in whom WG did not appear to involve the kidneys.[10] Currently, it is generally accepted that the diagnosis of WG requires the presence of granulomatous inflammation, focal necrosis, fibrinoid degeneration, and multinucleate giant cells occurring in a patient with the appropriate signs and symptoms.[9]

McDonald and his colleagues noted necrotizing epithelioid granulomas and vasculitis involving small arteries and veins in nasal samples obtained from 31 patients with WG.[2] Some of the granulomas had zones of fibrinoid necrosis while others contained microabscesses. The investigators did not, however, report how many of the samples manifested these features. Fauci and Wolff observed similar histologic findings in nasopharyngeal samples obtained from 10 patients with WG.[11] These workers described necrotizing granulomas with or without vasculitis in samples from six of the patients. Biopsy samples from the other four patients lacked specific inflammatory changes. Although Fauci and Wolff noted that nasopharyngeal symptoms predominated in virtually all of their patients, the diagnostic usefulness of the nasal biopsy was not evaluated.

Our study demonstrates that, as rigidly defined above, granulomatous vasculitis is not often observed in nasal mucosal samples obtained from patients with WG (four of 17 patients). To the extent that granulomatous vasculitis is an essential feature, nasal mucosal biopsy does not appear to be frequently diagnostic. In this regard, our experience is similar to that of Devaney and his coworkers. In a series of patients with WG, granulomatous vasculitis was observed by these investigators in just 7% of nasal specimens.[12] If the presence of nongranulomatous vasculitis is also considered indicative of WG, an additional three patients in our series may be regarded as having had diagnostic biopsies. Thus, seven of 17 patients with WG had diagnostic nasal or paranasal samples.

Fienberg[13,14] noted that extravascular necrosis or fibrinoid degeneration was usually present in WG and often accounted for much of the tissue destruction. His observation has recently received renewed emphasis.[15,16] Additionally, Mark, et al[16] have concluded from a study of 35 open lung biopsy samples that the earliest histologically visible lesion of WG is a small, usually extravascular, focus of collagen necrosis or fibrinoid degeneration.

Extravascular necrosis was observed in the present study almost as frequently as was vasculitis (six and seven patients, respectively). While peripheral palisades of histiocytes were not found about these extravascular foci, multinucleated giant cells were frequently present in adjacent areas. Although not specific, the presence of scattered multinucleated giant cells in 16 of the samples may serve as a helpful diagnostic clue in the absence of a vasculitis or clear-cut granulomatous inflammation.

Three patients had biopsy samples in which vasculitis was present in the absence of extravascular ne-

TABLE 2. Pathologic Findings

	G-V	N-GV	ENF	Vasculitis and ENF	Intimal Fibrosis	Giant Cells	Stromal Inflammation	Ulcers
No. of patients	4/17	3/17	6/17	4/17	7/17	10/17	16/17	13/17
No. of samples/biopsies	5/30	8/30	12/30	9/30	9/30	16/30	27/30	21/30

Abbreviations: G-V, granulomatous vasculitis; N-GV, nongranulomatous vasculitis; ENF, extravascular necrotic foci.

crosis. This observation differs from that of Fienberg who did not observe vasculitis in the absence of these extravascular foci.[14] Fienberg and McCluskey have stated that the diagnosis of WG can be established in many cases on the basis of biopsy specimens that do not demonstrate a vasculitis, but in which extravascular granulomas are present.[15] Samples from two of our patients contained micronecrotic foci in the absence of an active vasculitis. In light of the views of Fienberg and McCluskey, these samples could be considered as diagnostic of WG, thus raising to nine the number of patients in our study who had diagnostic nasal biopsy samples. To the extent that WG is not a primary vasculitis, we agree with this view. The specificity of these findings has not been thoroughly evaluated, however, and infectious agents should always be excluded by careful examination.

Current therapy has markedly improved the prognosis of WG, although severe side effects may on occasion complicate the clinical course.[1] While the diagnosis of WG rests upon characteristic clinical features, histologic confirmation is required to rule out other disorders which may closely mimic the signs and symptoms of WG, including infections, connective tissue disorders, Goodpasture's syndrome, and hypersensitivity vasculitis.[1,17] When compared with lung and renal biopsy, nasal mucosal biopsy is an innocuous method for obtaining tissue for histologic confirmation. Nevertheless, based upon our experience, nasal biopsy is of somewhat limited usefulness when only traditional histologic criteria are used to interpret them (41% of patients). In a clinical study of 77 patients with WG, Cordier et al[18] showed that patients died from WG primarily as a result of delays in diagnosis. The diagnostic efficacy of nasal biopsy is enhanced when extravascular foci of necrosis are regarded as diagnostic (52% of patients). This enhancement will help support this procedure as the initial diagnostic procedure of choice. In order to further maximize the usefulness of these biopsies, we recommend obtaining samples larger than 5 mm in diameter from areas away from ulcerated sites.

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