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Osamu Matsubara · Nobuyuki Yoshimura
Yasumasa Doi · Atsuhisa Tamura · Eugene J. Mark

Nasal biopsy in the early diagnosis of Wegener's (pathergic) granulomatosis

Significance of palisading granuloma and leukocytoclastic vasculitis

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Abstract The diagnostic value of the nasal biopsy in the early diagnosis of Wegener's granulomatosis and its value in prognosis were examined in 11 patients with a clinicopathological diagnosis of the disease. The vascular lesions found included microabscess in the vascular walls in 82%, leukocytoclastic capillaritis in 73%, fibrinoid necrosis of blood vessels in 45%, leukocytoclastic endovasculitis in 27%, and palisading granuloma in vascular wall in 9% of cases. The extravascular lesions included palisading granuloma in all cases, microabscess in 91%, and diffuse granulomatous tissues in 82%. Palisading microgranuloma (82%) was more frequent than palisading macrogranuloma (45%). After therapy, complete remission occurred in 8 patients, but 3 patients died of sepsis, diffuse pulmonary haemorrhage, and cerebral haemorrhage. Comparison of the frequency of each finding in the nasal biopsy specimens between patients who achieved remission and those who died showed that leukocytoclastic vasculitis was found more commonly in fatal cases, and leukocytoclastic endovasculitis was observed only in fatal cases. Palisading granuloma as a vascular or extravascular lesion is the primary and most important finding in a histopathological diagnosis of Wegener's granulomatosis, microabscess in vascular walls is a secondary but the next most important finding, and leukocytoclastic vasculitis heralds dissemination of the disease and poor prognosis. It requires aggressive therapy.

Key words Nasal mucosa · Wegener's granulomatosis · Diagnosis · Pathology · Vasculitis

O. Matsubara (✉)
Department of Pathology, National Defense Medical College,
3-2 Namiki, Tokorozawa, Saitama, 359 Japan
Tel.: (81) 429-95-1211, ext. 2277; Fax: (81) 429-95-0638

O. Matsubara · N. Yoshimura · Y. Doi · A. Tamura
Department of Pathology, Faculty of Medicine,
Tokyo Medical and Dental University, Yushima, Tokyo, Japan

E.J. Mark
Department of Pathology, Massachusetts General Hospital,
Boston, Massachusetts, USA

Introduction

Wegener's (pathergic) granulomatosis is a systemic disease which classically affects the upper respiratory tract, lung and kidney [10, 15]. Historically, autopsy pathology provided most of the tissue for morphological investigation. Since prompt treatment with immunosuppressive and cytotoxic agents can modify or eliminate the aggressive course of this disease [6], clinicians and pathologists should not wait for the development of the classic triad of organ involvement to appear before making the diagnosis. The nasal mucosa is frequently involved in Wegener's granulomatosis [7] and is an easily accessible site for biopsy, for which reason accurate interpretation is important. We here evaluate the diagnostic information contained in the nasal biopsy in a patient with suspected Wegener's granulomatosis and correlate it with prognosis.

Materials and methods

The files of the Laboratory of Surgical Pathology of the Tokyo Medical and Dental University Hospital were searched for all nasal mucosal biopsies from patients with Wegener's granulomatosis over the period 1970–1991. We reviewed all of the pathological material of 22 patients with a clinical, pathological or clinicopathological diagnosis of Wegener's granulomatosis. There were 35 biopsies of nasal mucosa, 13 biopsies of mucosa of paranasal sinuses, 8 transbronchial biopsies of lung, 4 needle biopsies of kidney, and 3 biopsies of skin. Thirteen cases came from patients seen at the above University Hospital and 9 cases were from consultations from other hospitals.

All cases were studied histologically with haematoxylin-eosin-stained slides. Most of the cases were studied also with additional histochemical stains, including elastic tissue, Masson's trichrome, reticulum, periodic acid-Schiff, acid fast, methenamine silver, and phosphotungstic acid-haematoxylin. These special stains had been performed for various reasons but primarily to study blood vessels and to exclude infection. Mycobacterial and fungal infections were excluded by culture.

Of the 22 patients, the nasal biopsies in 11 patients with a clinical diagnosis of Wegener's granulomatosis were not histopathologically consistent with this disease. Three cases had T-cell lymphoma of nasopharyngeal origin, 2 cases had nasal tuberculosis,

Table 1 Clinical findings of 11 cases of nasal Wegener's granulomatosis (*CP* cyclophosphamide, *P* prednisone, *DPH* diffuse pulmonary haemorrhage, *CH* cerebral haemorrhage)

Case no.	Age/sex	Presenting signs/symptoms	Period to biopsy	ELK class	Therapy	Outcome
1	19/F	Headache, nasal obstruction	3 months	E	CP	Remission
2	38/F	Fever, lung infiltrates	1.5 months	EL	CP+P	Remission
3	23/F	Nasal discharge, epistaxis, nasal obstruction, hearing loss	3 years	E	CP+P	Remission
4	27/F	Malaise, lung infiltrates	8 months	ELK	CP+P	Remission
5	53/F	Nasal obstruction, epistaxis	1 year, 4 months	EL	CP+P	Remission
6	71/F	Fever, nasal discharge, epistaxis	1 month	E	CP+P	Remission
7	22/M	Lung infiltrates	1 month	EL	CP+P	Remission
8	45/F	Fever, sore throat	3 months	E	CP+P	Remission
9	46/F	Rhinorrhoea, headache, nasal obstruction	2–3 years	ELK	P	Death (sepsis)
10	61/M	Rhinorrhoea, hearing loss, cough, sputum	1 year, 2 months	ELK	CP+P	Death (DPH)
11	68/M	Rhinorrhoea, epistaxis	1 month	ELK	CP+P	Death (CH)

and 6 cases had chronic non-specific rhinitis. The remaining 11 cases with clinicopathological features characteristic of Wegener's granulomatosis comprised the body of the study.

Results

Clinical

Four patients were male and 7 were female with an average age of 43 years (range 19–71 years). Eight patients had signs and symptoms from the upper respiratory tract, 3 patients had lung infiltrates on chest radiographs, and 2 patients had hearing loss. Nine patients were treated with corticosteroids and cyclophosphamide, 1 patient was treated with corticosteroids alone (case 9), 1 patient was treated with cyclophosphamide and radiation therapy to the nasal sinuses (case 1). Clinical follow-up ranged from 1 month to 18 years. Complete remission occurred in 8 patients. One patient had a healthy baby while in remission (case 4). One patient (case 5) died of colonic carcinoma after being in remission for 15 years. One patient died of sepsis, 1 died of diffuse pulmonary haemorrhage, and 1 died of cerebral haemorrhage unrelated to Wegener's granulomatosis. Case 10 has been reported previously [17]. The clinical findings are summarized in Table 1.

Pathological

The nasal biopsies ranged in size from 2 to 7 mm in greatest dimension. The tissue consisted of oedematous and inflamed lamina propria up to 2 mm in thickness covered by a single layer of columnar epithelial cells. The lamina propria contained arterioles and venules in addition to capillaries but rarely arteries of veins, or identification of vasculitis using the criterion of vessel wall destruction was problematic or precluded in such samples.

Following previous experience which emphasizes recognition of micronecrosis and palisading granuloma for the early diagnosis of Wegener's granulomatosis in the lung [12], we analysed the cases in terms of the type of necrosis and inflammation, the location of disease within the nasal mucosal microanatomy, separation into vascular and extravascular (parenchymatous) lesions, and associated reactions.

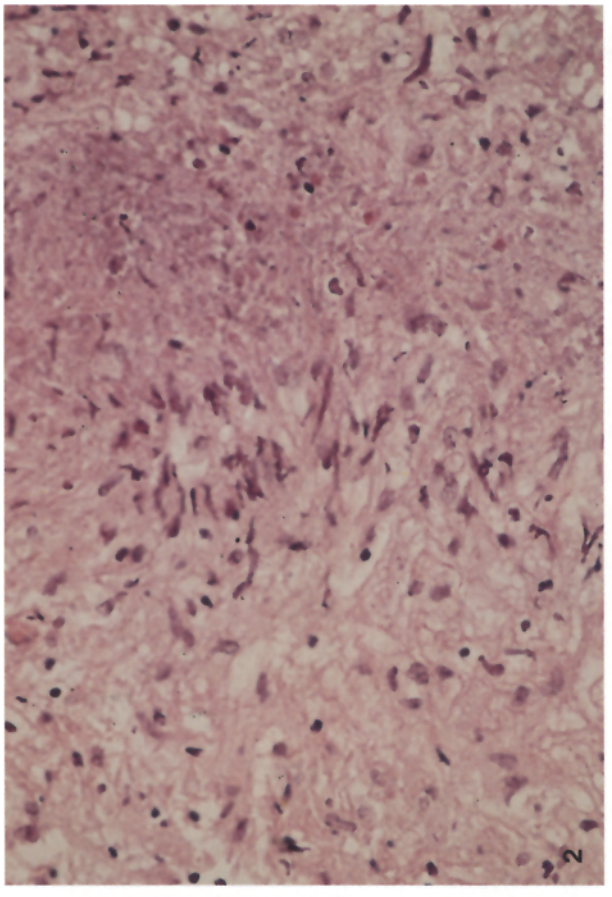
Palisading granuloma (Figs. 1, 2) was defined [12] as an aggregate of histiocytes whose elongated nuclei had long axes parallel to each other and perpendicular to a nidus containing neutrophils, and nuclear dust. The palisading granuloma was observed in both vascular (Fig. 3) and extravascular lesions. We separated palisading granuloma into palisading microgranuloma (<1 mm) and palisading macrogranuloma (>and =1 mm). We defined leukocytoclastic endovasculitis (Fig. 4) as marked polymorphonuclear and mononuclear infiltration of the intima, associated with fibrinoid necrosis, nuclear dust and narrowed lumen but without prominent transmural inflammation. We defined leukocytoclastic capillaritis (Fig. 5) as fibrinoid necrosis of walls of capillaries associated with neutrophils and nuclear dust as previously defined in the lung [11, 12]. We defined diffuse granulomatous tissue as sheets or tentacles of epithelioid histiocytes including multinucleated giant cells associated with lymphocytes, plasma cells, or eosinophils.

Fig. 1 Palisading microgranuloma consisting of an aggregate of histiocytes whose elongated nuclei had long axes parallel to each other and perpendicular to a nidus containing neutrophils, and nuclear dust. Inflamed nasal glands in the left lower corner. H & E stain, ×185

Fig. 2 A part of the palisading macrogranuloma with an aggregate of histiocytes. Necrosis on the right. H & E stain, ×480

Fig. 3 Palisading microgranuloma in a vascular wall with a narrowed lumen. H & E stain, ×185

Fig. 4 Leukocytoclastic endovasculitis is characterized by marked polymorphonuclear and mononuclear infiltration to the intimal side of the vascular walls, associated with nuclear dusts and narrowed lumen. H & E stain, ×220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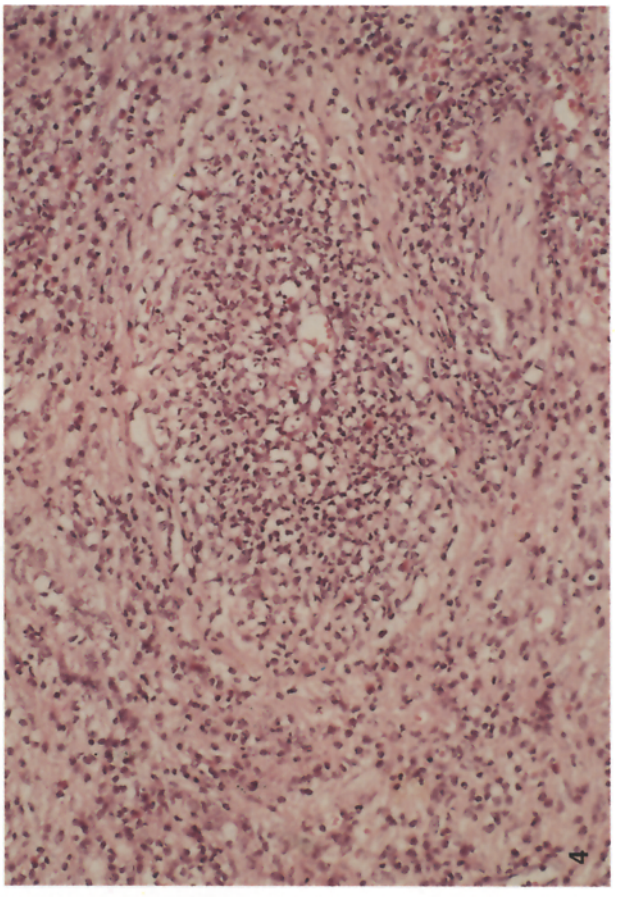
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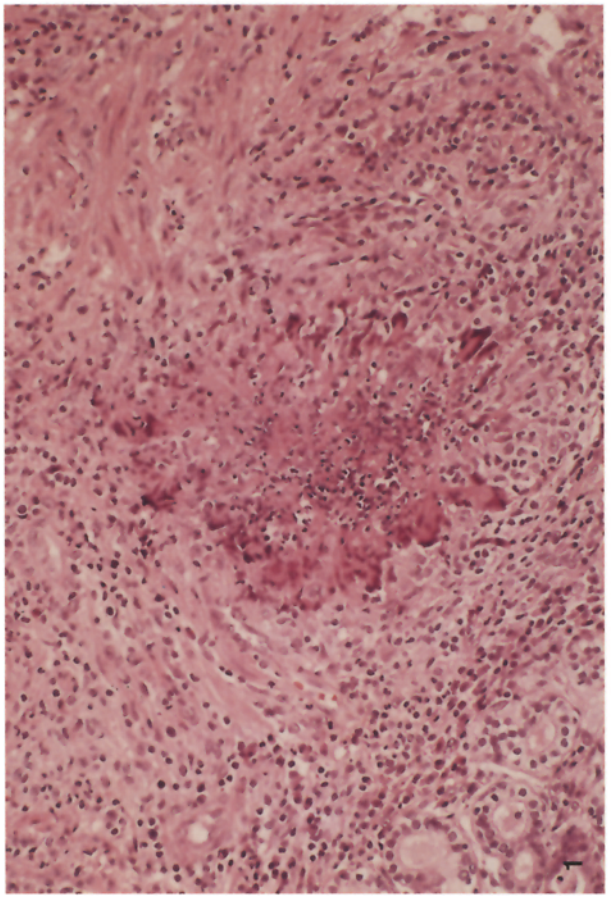
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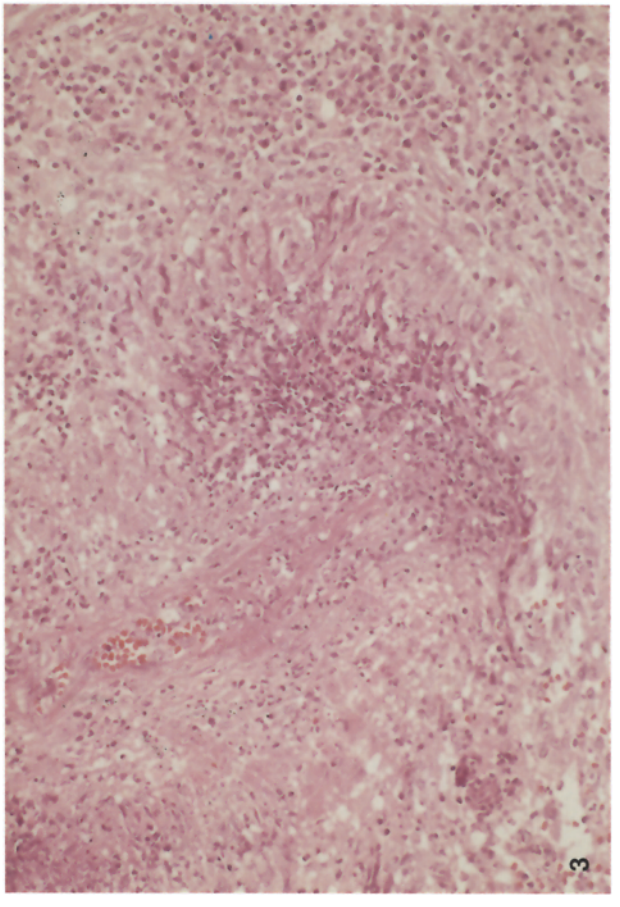
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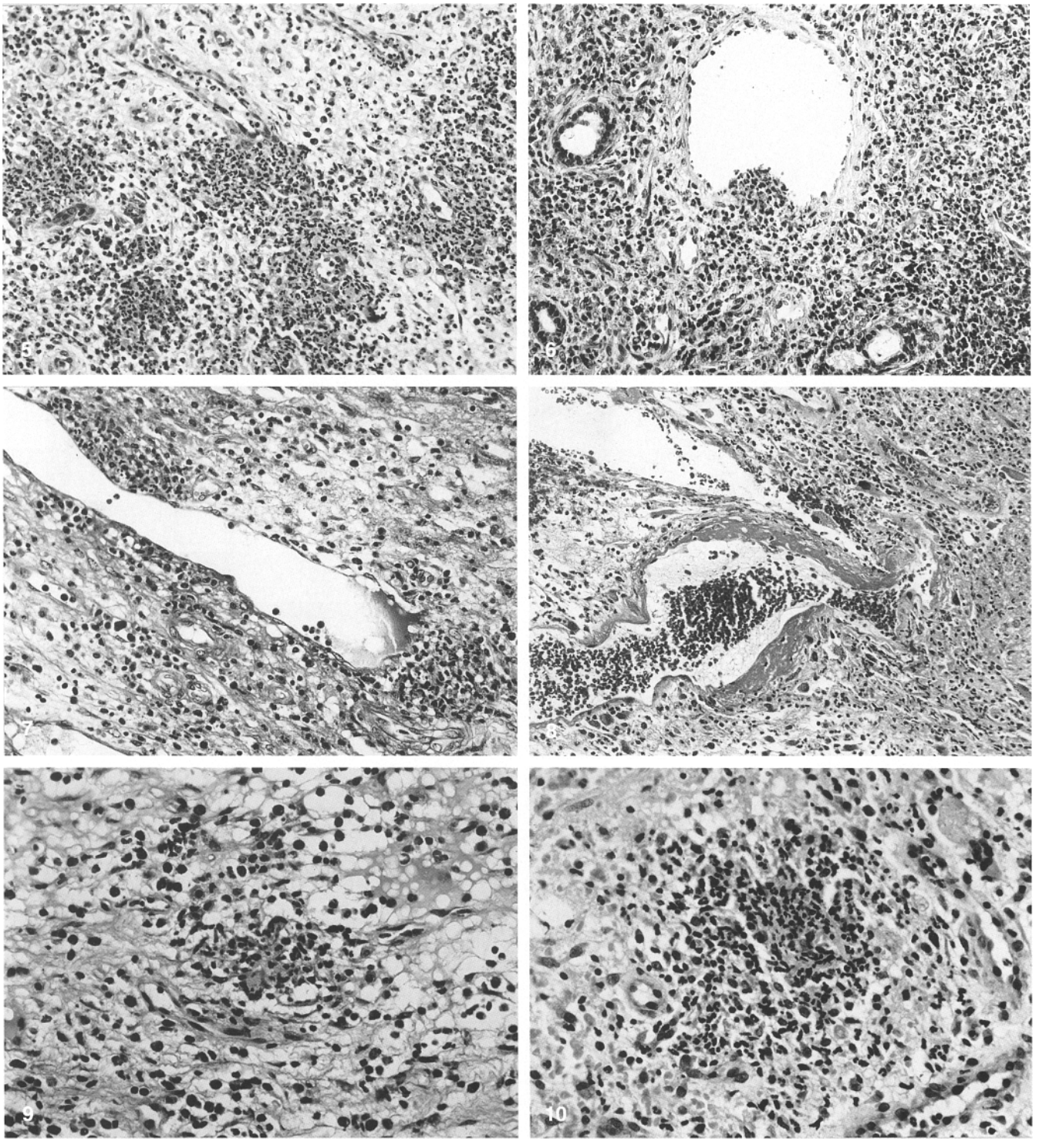

Fig. 5 Leukocytoclastic capillaritis with an accumulation of neutrophils and nuclear dusts in and around walls of capillaries. H & E stain, ×130

Fig. 6 Microabscess in a venule (cross-section). H & E stain, ×200

Fig. 7 Microabscess in a venule (longitudinal section). H & E stain, ×210

Fig. 8 Fibrinoid necrosis of blood vessels and leukocytic infiltration with multinucleated giant cells in the parenchyma. H & E stain, ×500

Fig. 9 Smaller lesion in which a tiny necrotic focus is surrounded by polymorphous leukocytes, histiocytes and two multinucleated giant cells. H & E stain, ×170

Fig. 10 Larger microabscess with a few histiocytes and no obvious multinucleated giant cells. H & E stain, ×170

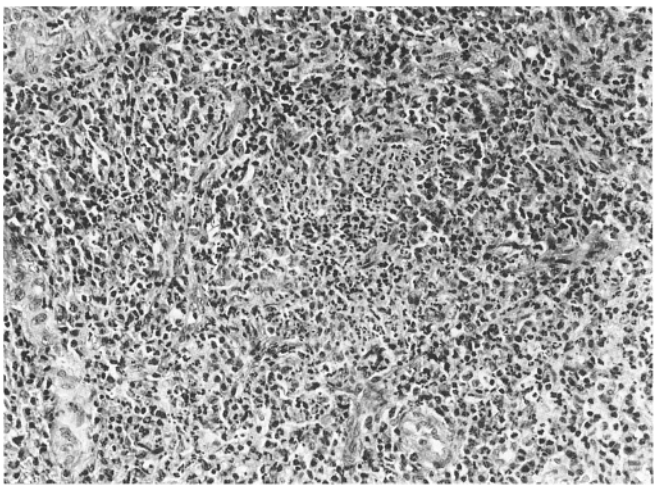

Fig. 11 Microabscesses in the parenchyma in mucosal biopsy specimen. H & E stain, ×110

Arterial and venous involvement took several forms: microabscess in the wall, fibrinoid necrosis, lymphohistiocytic infiltrate, palisading granuloma, leukocytoclastic endovasculitis, leukocytoclastic capillaritis and fresh or organized thrombosis. Two or more of these changes were present in each case. Microabscess was identified in the vascular walls of venules (Figs. 6, 7), arterioles, and small muscular arteries in 9 cases (82%). Leukocytoclastic capillaritis was identified in 8 cases (73%), fibrinoid necrosis of blood vessels (Fig. 8) in 5 cases (45%), leukocytoclastic endovasculitis in 3 cases (27%), and palisading granuloma in the wall in one case (9%) (Fig. 3).

Extravascular lesions also took several forms: palisading granuloma, diffuse granulomatous tissue with multinucleated giant cells, microabscess and neutrophilic infiltration of mucous glands. Palisading granuloma was seen in all cases, while palisading microgranuloma (82%) was more frequent than palisading macrogranuloma (45%). Palisading microgranuloma could be seen in its entirety because of the small size of the biopsy specimens, appearing as a tiny necrotic focus surrounded by leukocytes and histiocytes (Figs. 9, 10), whereas only a portion of a palisading macrogranuloma might appear in the specimen. Sometimes a palisading granuloma seemed to evolve from a microabscess. Microabscesses (91%) (Fig. 11) and diffuse granulomatous tissue (82%) were both very common. Necrosis (91%), eosinophilia (91%) and haemosiderin deposition (27%) were associated reactions.

The histopathological findings in the nasal biopsies are summarized in Table 2.

We also compared the frequency of each finding in the nasal biopsies from patients who achieved remission and from those who died. Leukocytoclastic vasculitis was more common in fatal cases. Leukocytoclastic endovasculitis was observed only in fatal cases. There was no difference of the frequency of other findings between the two groups.

Table 2 Histological findings and prognostic features in 11 cases of nasal Wegener's granulomatosis

	Outcome													Total
	Remission									Fatal				
	Case no.									Case no.				
	1	2	3	4	5	6	7	8	(%)	9	10	11	(%)	(%)
Vascular lesions														
Microabscess in vascular wall	+	+	+	0	+	+	+	0	75	+	+	+	100	82
Fibrinoid necrosis	+	+	+	0	0	0	0	+	50	0	0	+	33	45
Lymphohistiocytic infiltrate	0	0	+	+	0	+	+	0	50	+	0	0	33	45
Fresh or organized thrombosis	+	0	+	0	0	0	0	0	25	0	0	0	0	18
Palisading granuloma	0	0	0	0	0	0	0	0	0	+	0	0	33	9
Leukocytoclastic endovasculitis	0	0	0	0	0	0	0	0	0	+	+	+	100	27
Leukocytoclastic capillaritis	0	0	0	+	+	+	+	+	63	+	+	+	100	73
Extravascular lesions														
Palisading granuloma	+	+	+	+	+	+	+	+	100	+	+	+	100	100
Palisading microgranuloma	+	0	+	+	+	+	+	0	75	+	+	+	100	82
Palisading macrogranuloma	+	+	0	0	0	0	0	+	38	+	+	0	66	45
Diffuse granulomatous tissue with multinucleated giant cells	0	+	+	+	+	+	+	0	75	+	+	+	100	82
Microabscess	0	+	+	+	+	+	+	+	88	+	+	+	100	91
Neutrophilic infiltration to nasal glands	+	0	+	0	+	+	+	+	75	+	+	+	100	82
Associated reactions														
Necrosis	+	+	+	+	+	+	+	+	100	+	0	+	66	91
Eosinophilia	0	+	+	+	+	+	+	+	88	+	+	+	100	91
Haemosiderin	0	0	0	+	+	0	0	0	25	0	+	0	33	27

Discussion

Wegener's granulomatosis may be a clinical, histopathological or clinicopathological diagnosis. In this work we focus on the utility of nasal biopsy to provide a histopathological diagnosis without waiting for clinical or pathological evidence of disease in other organs. As in the lung [12], we find that in the nasal and sinus mucosa palisading granuloma and microabscess are the most discriminating features for the pathological diagnosis of Wegener's granulomatosis. These two features can be observed in both vascular and extravascular locations. We do not believe that these lesions must be located in blood vessels to establish the diagnosis.

After reviewing 30 nasal biopsy specimens from 17 patients, Del Buono and Flint [2] reported the frequency of granulomatous vasculitis, non-granulomatous vasculitis, extravascular necrotic foci, and giant cells as 4/17 (24%), 3/17 (18%), 6/17 (35%), and 10/17 (59%), respectively. Colby et al. [1] added their own data of 28 biopsies to the 30 biopsies of Del Buono and Flint, and reported the frequency of vasculitis, necrosis, giant cells, eosinophils, and microabscess as 28/58 (48%), 31/58 (53%), 30/58 (52%), 39/58 (67%), and 19/28 (68%), respectively. Devaney et al. [4] reviewed a series of 126 biopsies of the head and neck region in 70 patients and reported the frequency of granulomatous vasculitis, geographic necrosis, giant cells, and microabscess as 4/60 (7%), 12/60 (20%), 28/60 (47%), and 20/60 (33%), respectively.

Pathologists around the world have different concepts of vasculitis and the factors necessary to make the diagnosis of Wegener's granulomatosis. Mark et al. [12] described the various types of vascular lesions seen in the lung biopsy in Wegener's granulomatosis. Devaney et al. [4] also described various vascular lesions in biopsies of the sinuses. In both studies granulomatous vasculitis was infrequent. We use the term granulomatous vasculitis to describe palisading granuloma or palisading histiocytes in the walls of blood vessels, but we do not believe that such vasculitis is essential for the pathological diagnosis of Wegener's granulomatosis. Rather, we find that microabscesses are more frequent and identified with ease, and thus more often decisive in the early histopathological diagnosis in the nasal and sinus biopsy.

Infectious processes giving rise to pus or granulomas must be differentiated from the microabscesses seen in Wegener's granulomatosis. As defined here and elsewhere [12], palisading granuloma should be distinguished from a compact, rounded circumscribed granuloma. The latter, of tuberculoid or sarcoidal type, consists of aggregates of histiocytes and may undergo central fibrinous or caseous necrosis. We believe necrosis constitutes the primary event in the formation of the palisading granuloma of Wegener's granulomatosis in nasal mucosa as well as lung whether or not it involves vascular walls. We support Fienberg's suggestion [8] that the palisading granuloma is the single most important observation leading to the diagnosis of Wegener's (pathergic) granulomatosis and is virtually pathognomonic of the disease.

Necrosis in nasal biopsies is variable and of little value by itself for a specific diagnosis, because the biopsies are usually small, ulcerated and inflamed. Del Buono and Flint [2] recommended obtaining samples larger than 5 mm in diameter from areas away from ulcerated sites. The nasal mucosa may heal quickly, and an initial biopsy of a healing or healed phase of the disease display only non-specific inflammation, so repeat biopsies have been useful. Deeper cuts or serial sections are useful for tiny specimens. The nasal cavity and paranasal sinuses are rarely examined at autopsy, and we might learn more about Wegener's granulomatosis if the sinuses were studied in more detail when the opportunity arises.

The relationship between antineutrophil cytoplasmic antibodies (ANCA) and Wegener's granulomatosis was recognized by van der Woude et al. [16] and confirmed by others [13, 14]. The target antigen is identified as proteinase 3, a neutral serine protease which is localized in azurophilic granules of neutrophils. ANCA is now subdivided as that which shows cytoplasmic staining (c-ANCA), and perinuclear staining (p-ANCA). Reactions of p-ANCA are directed against myeloperoxidase, elastase, and other lysosomal enzymes [5]. The specificity of c-ANCA for Wegener's granulomatosis has ranged from 67% to 98%, so a negative c-ANCA test does not rule out the disease. Fienberg et al. [9] stated that correlation of clinical and histological findings remains the only definitive method of diagnosis in patients with negative tests for ANCA and that histopathological examination of tissue remains the gold standard.

ELK classification [3] (upper airway or ear, nose, and throat – E, lung – L, kidney – K) is used for convenience to express the anatomical extent of Wegener's granulomatosis. This classification ties together the classic triad and limited forms of the disease. Why the disease remains localized in some patients without treatment and disseminates in others even with treatment remains to be clarified.

In summary, we describe the histopathological spectrum of the nasal mucosal biopsies of the patients with Wegener's granulomatosis. Palisading granuloma as a vascular or extravascular lesion is the most distinctive lesion, followed by microabscess in vascular walls and leukocytoclastic vasculitis. Furthermore, the type of lesion has prognostic importance. Leukocytoclastic vasculitis and especially leukocytoclastic endovasculitis indicate poor prognosis, because they were observed much more frequently in fatal cases. Leukocytoclastic endovasculitis is a morphological hallmark that portends disseminating disease and requires aggressive medical therapy.

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References

1. Colby TV, Tazelaar HD, Specks U, DeRemee RA (1991) Nasal biopsy in Wegener's granulomatosis. Hum Pathol 22: 101–104
2. Del Buono EA, Flint A (1991) Diagnostic usefulness of nasal biopsy in Wegener's granulomatosis. Hum Pathol 22:101–104
3. DeRemee RA, McDonald TJ, Harrison EG Jr, Coles DT (1975) Wegener's granulomatosis. Anatomic correlates, a proposed classification. Mayo Clin Proc 51:778–781
4. Devaney KO, Travis WD, Hoffman G, Leavitt RY, Lebovics R, Fauci AS (1990) Interpretation of head and neck biopsies in Wegener's granulomatosis. A pathologic study of 126 biopsies in 70 patients. Am J Surg Pathol 14:555–564
5. Falk RL, Jennette JC (1988) Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. N Engl J Med 318:1651–1657
6. Fauci AS, Wolff SM, Johnson JS (1971) Effect of cyclophosphamide upon the immune response in Wegener's granulomatosis. N Engl J Med 285:1493–1496
7. Fauci AS, Haynes BF, Katz P, Wolff SM (1983) Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 98:76–85
8. Fienberg R (1989) A morphologic and immunohistologic study of the evolution of the necrotizing palisading granuloma of pathergic (Wegener's) granulomatosis. Semin Respir Med 10:126–132
9. Fienberg R, Mark EJ, Goodman M, McCluskey RT, Niles JL (1993) Correlation of antineutrophilil cytoplasmic antibodies with the extrarenal histopathology of Wegener's (pathergic) granulomatosis and related forms of vasculitis. Hum Pathol 24:160–168
10. Godman GC, Churg J (1954) Wegener's granulomatosis. Pathology and review of the literature. AMA Arch Pathol 58: 33–553
11. Mark EJ, Ramirez JF (1985) Pulmonary capillaritis and hemorrhage in patients with systemic vasculitis. Arch Pathol Lab Med 109:413–418
12. Mark EJ, Matsubara O, Tan-Liu NS, Fienberg R (1988) The pulmonary biopsy in the early diagnosis of Wegener's (pathergic) granulomatosis. Hum Pathol 19:1065–1071
13. Noelle B, Specks U, Luedemann J, Rohrbach MS, DeRemee RA, Gross WL (1989) Anticytoplasmic autoantibodies: their immunodiagnostic value in Wegener's granulomatosis. Ann Intern Med 111:28–40
14. Rasmussen N, Wiik A, Permin H (1989) Detection and clinical implications of antineutrophil cytoplasm antibodies. Semin Respir Med 10:149–155
15. Wegener F (1939) Über eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arteriensystems und der Nieren. Beitr Pathol Anat 102:36–68
16. Woude FJ van der, Lobatto S, Permin H, Van der Giessen M, Rusmussen N, Wiik A, Vas Es LA, Van den Her GK, The TH (1985) Autoantibodies against neutrophils and monocytes: tools for diagnosis and marker of disease activity in Wegener's granulomatosis. Lancet I:425–429
17. Yoshimura N, Matsubara O, Tamura A, Kasuga T, Mark EJ (1992) Wegener's granulomatosis associated with diffuse pulmonary hemorrhage. Acta Pathol Jpn 42:657–661