CONFERENCIA CLÍNICO-PATOLÓGICA

EXOFTALMOS Y MENINGITIS CRÓNICA EN UN VARÓN DE 49 AÑOS

Dr. Antonio Vidaller
Medicina Interna
Sitges - 2007

MENINGITIS CRÓNICA EN UN VARÓN DE 49 AÑOS

Varón de 49 a. con meningitis crónica de 1 año y medio de duración que presenta exoftalmos ojo izdo. motivo por el cual se traslada a nuestro hospital.

Un año y medio antes presentó:

- Parálisis facial dcha.
- Hipoacusia, vértigo
- Dolor en hemicara dcha.

} **Ingreso hospitalario**

EXPLORACIONES COMPLEMENTARIAS:

- TAC y RNM craneal: normales
- LCR: normal
- Analítica general: normal
- Serología Brucella sp++

TRATAMIENTO:

- Doxicilina
- Rifampicina

} NO RESPUESTA

6 MESES DESPUÉS DEL INGRESO

- Hipoacusia izda.
- ↓ Agudeza visual bilateral y diplopia

Exploración:

- Amaurosis dcha.
- ↓ agudeza visual izda.
- Parálisis facial bilateral
- Neuralgia de la 1ª y 2ª rama del trigémino izdo.
- Hipoacusia bilateral
- ROMBERG (+) con lateropulsión dcha.

Resto de exploración física general y neurológica normal

- La TC craneal demostró: captación difusa de contraste en la tienda del cerebelo (1).
- PL: LCR claro presión 20cmH2O
- Proteínas 119 gr/l
- Glucosa 70 mg/dl (glucosa 93 mg/ml) sangre
- Células 98/mm^3 (100% linfos)
- GRAM y cultivo (-)
- ZN (-)
- Hongos (-)
- Serologías Brucella Borrelia. Herpes virus y LUES (-) (en LCR)

Analítica General:

Hb 110 gr./l, Plaquetas 540.000, VSG 105, F.A. 494, gGT 357 ↑, Rosa Bengala (+), Coombs Brucella +, 1/40 y 1/640 respectivamente.

Resto de serología en sangre: Clamydia psitacci, Mycoplasma, legionella , Coxiella Burnetti y Toxoplasma (-).

PPD (-)

Rx. Tórax: Lesión apical izda. de aspecto residual

Meningitis crónica

Se inicia tto. con: Cotrimoxazol y Dexametasona.

Evolución: discreta mejoría del estado general y de la cefalea.

A las 3 semanas y media: fiebre y empeoramiento de la cefalea.

Nueva PL: LCR claro: presión 28cmH_2O, Proteinas: 120 gr/l, Células 198/mm^3

Se cambió a tto. triple con:

ISONIALIDA
RIFAMPICINA
PIRAZINAMIDA

Empeoramiento de la cefalea, nauseas y vómitos.

Aparece 1 semana después:

- Edema palpebral izdo.
- Quemosis conjuntival
- Exoftalmos izdo.

TAC Órbitas: ocupación región posterior ambas órbitas.

RNM SNC: Engrosamiento meningeo que se realzaba intensamente tras la administración de contraste. Dichas alteraciones afectaban a la hoz de cerebelo tentorio, senos cavernosos y ambos nervios ópticos.

Se traslada a nuestro centro (HUB) a NEURO-OFTALMOLOGÍA.

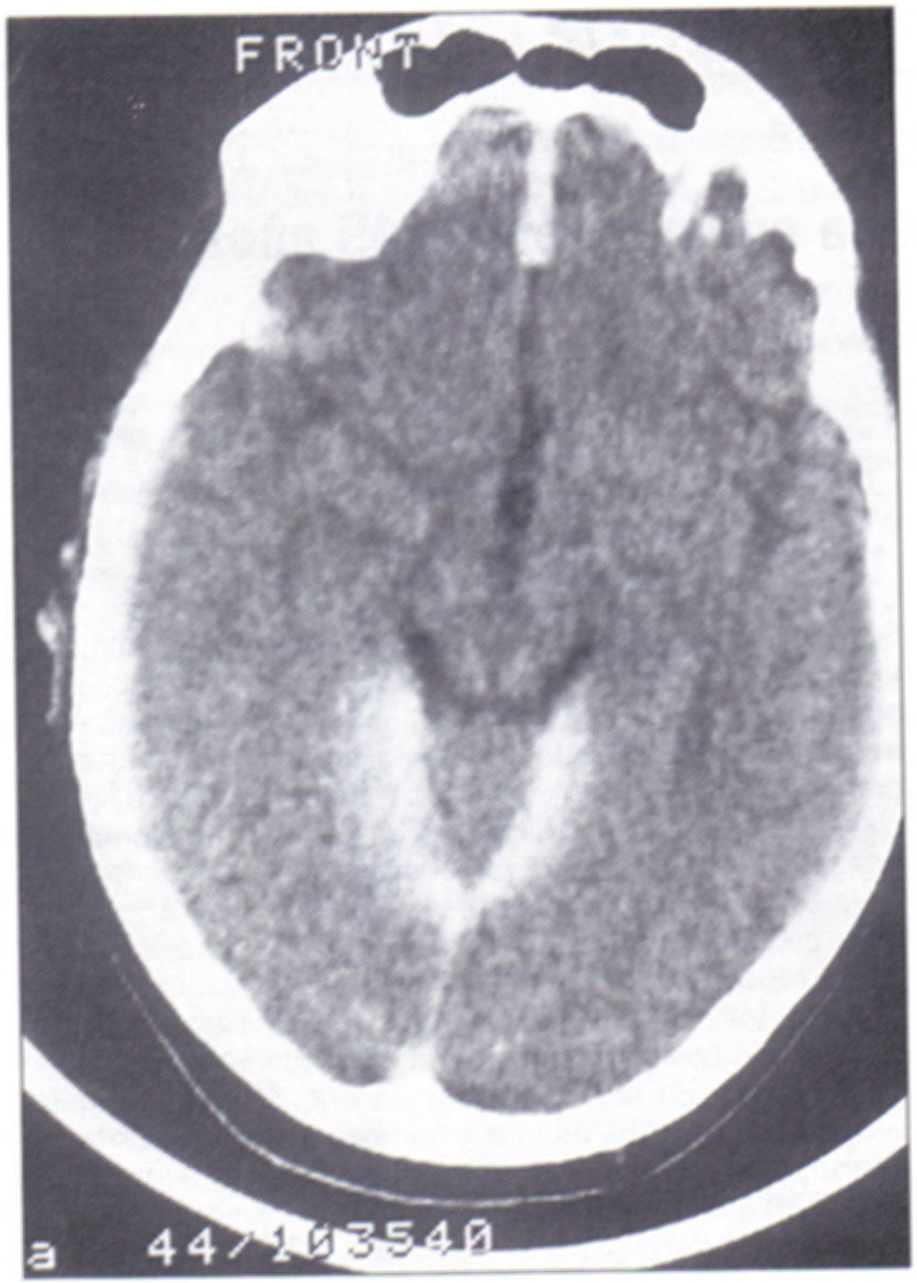


Fig. 1. TC craneal después de la administración de contraste intravenoso. Se observa engrosamiento y captación de las meninges en el tentorio.

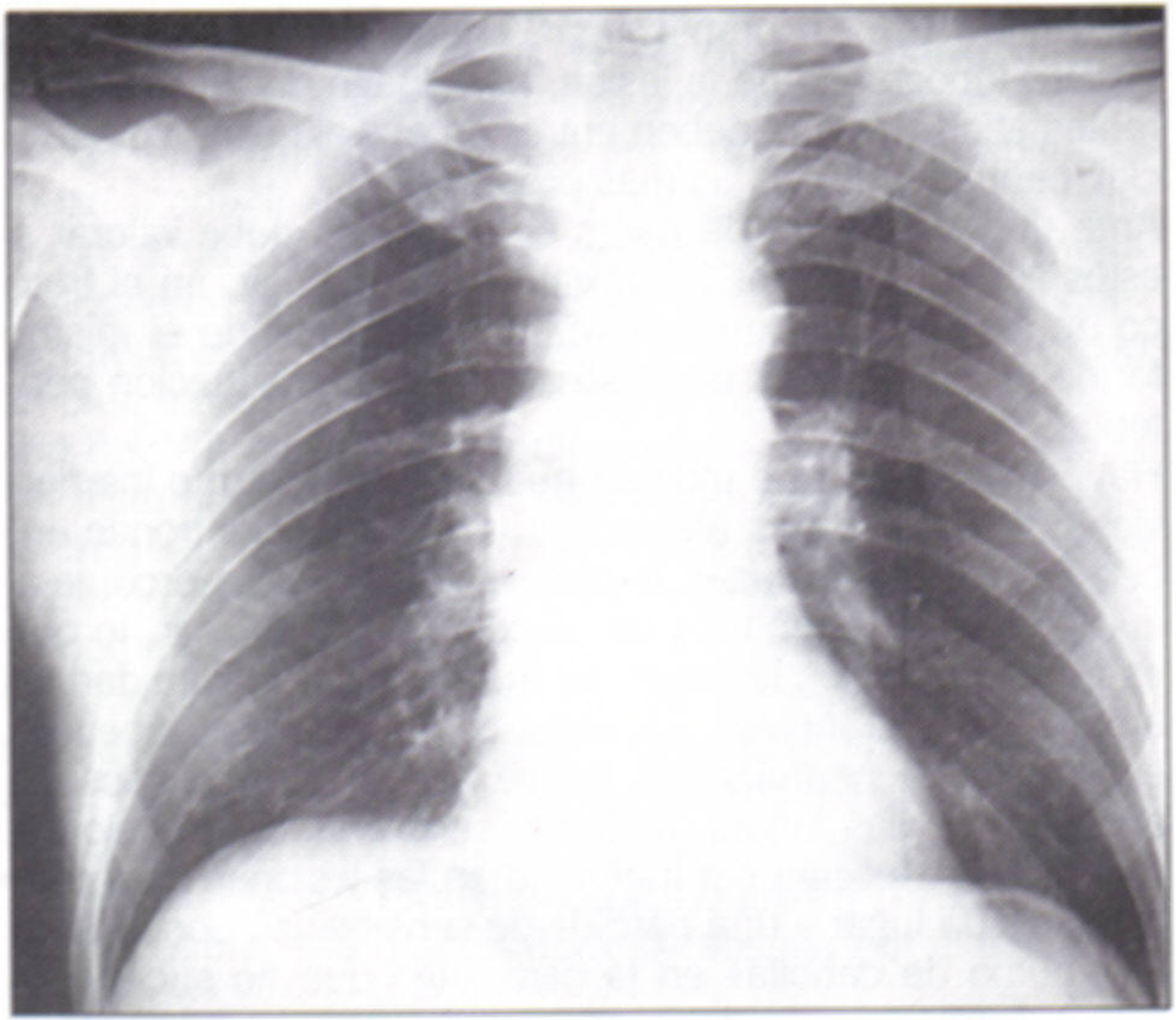


Fig. 2. Radiografía de tórax. Silueta cardíaca y contornos mediastínicos normales. No se observan lesiones del parénquima pulmonar. Tan sólo destaca un discreto engrosamiento de la pleura apical izquierda.

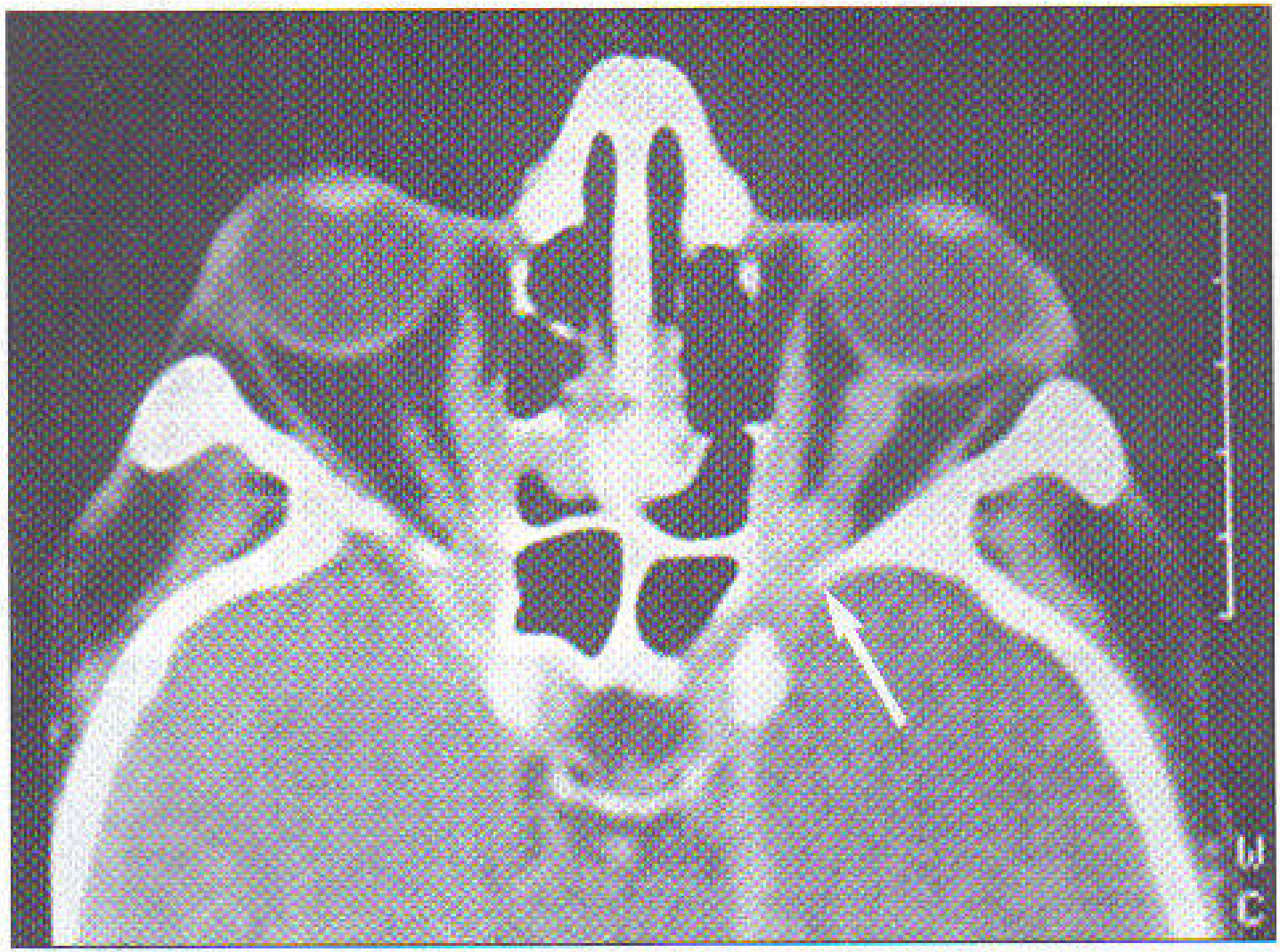


Fig. 3. TC orbitaria. Cortes axiales de la órbita después de la administración de contraste intravenoso. En los cortes más inferiores se puede observar la persistencia de engrosamiento y captación meníngea en el tentorio y en el agujero óptico (flecha).

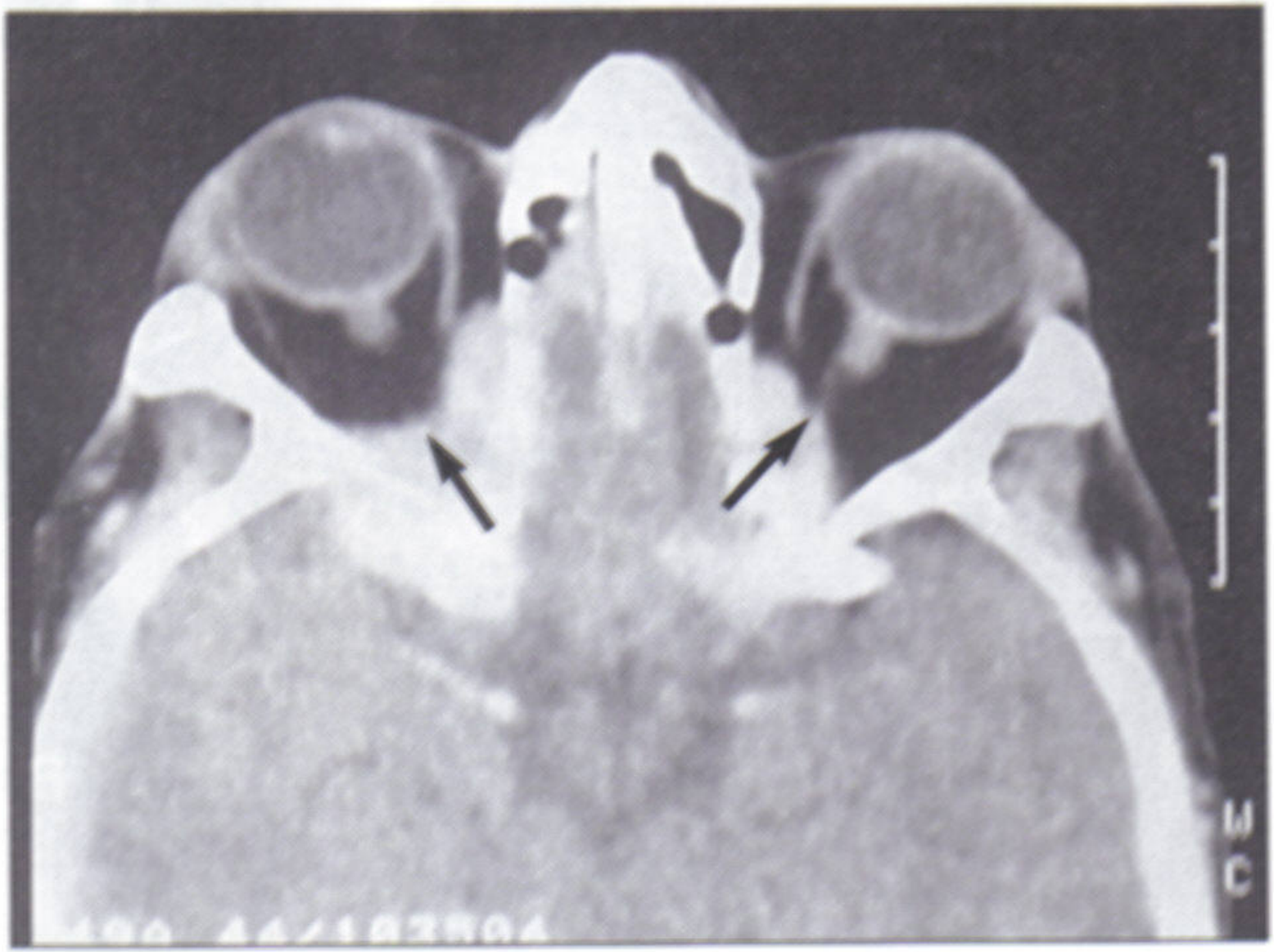


Fig. 4. TC orbitaria. En los cortes más superiores se observa una infiltración de la grasa orbitaria extraconal que capta contraste (flechas).

Exploración en nuestro centro (HUB)

Moderada afectación del estado general, TA 180/100, Tª 37ºC, FC 100x'.

- Amaurosis bilateral con atrofia óptica
- Cofosis bilateral
- Exoftalmos izdo.

Resto exploración física general: Normal

Analítica: VSG 40, Hties 3'36x10^{12}, Hb 104 g/l, VCM 89, Leucocitos 12.000 (65S, 28L, 4M), Plaquetas 482.000

Se practicó nueva PL: LCR claro: presión 30cm H_2O, Prot. 1'69, Glucosa 3'7, Células 200 95% linfos.

Citología: Normal

Gram y cultivo (-)

Serologías en LCR: Brucella, Lues, Borrelia (-)

Criptococo (-)

ZN (-)

TAC Toracoabdominal:

- Lesiones fibróticas en vértice pulmonar dcho.
- Lesión hepática calcificada (posible granuloma)

Potenciales visuales y auditivos: no se obtuvo respuesta

RM Craneal: Infiltración de la grasa de ambas órbitas y engrosamiento meningeo de predominio basal.

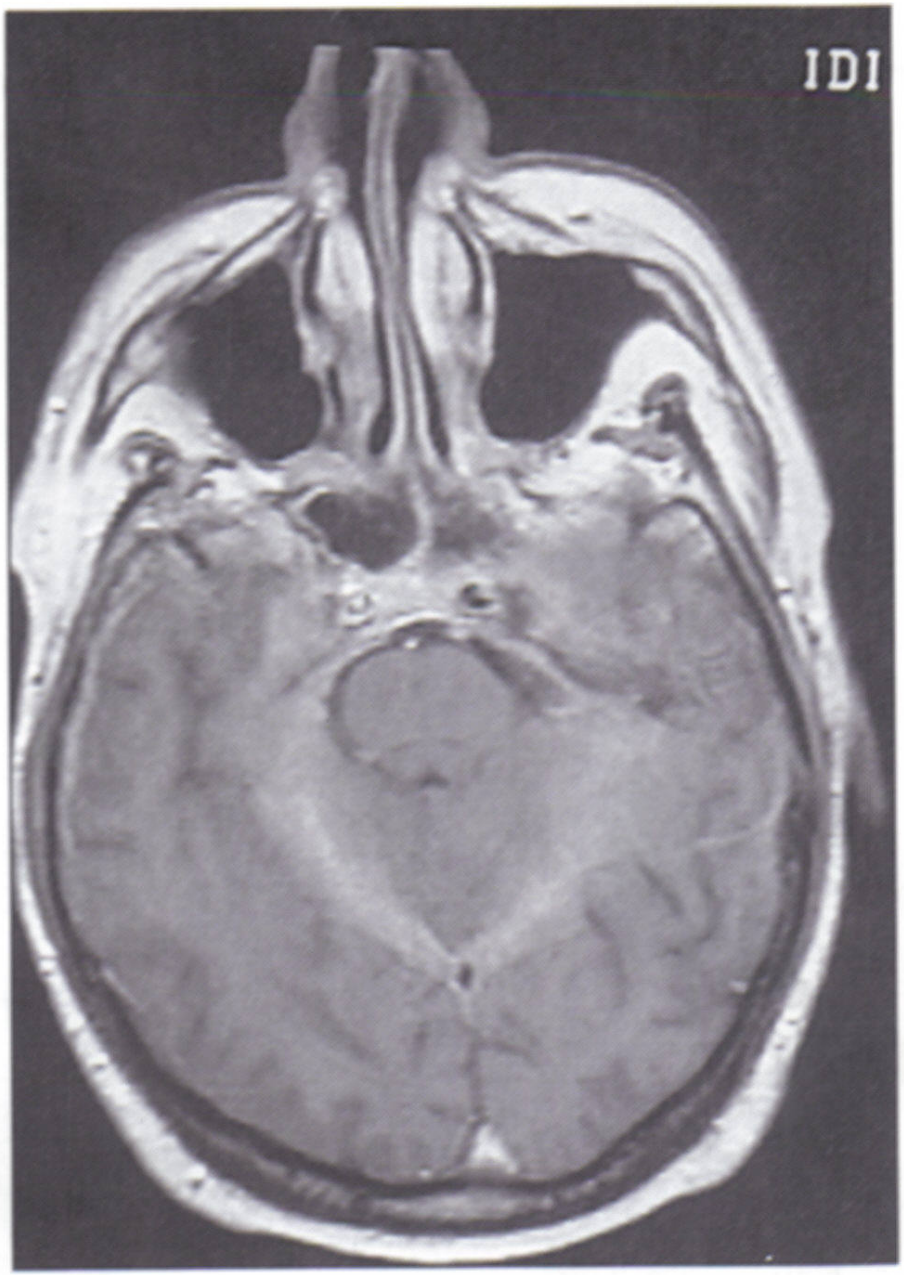


Fig. 5. RM craneal. Cortes axiales en secuencia potenciada en T_1 después de la administración de contraste intravenoso. Engrosamiento y captación de la duramadre en el tentorio y en la parte anterior de la hoz del cerebro.

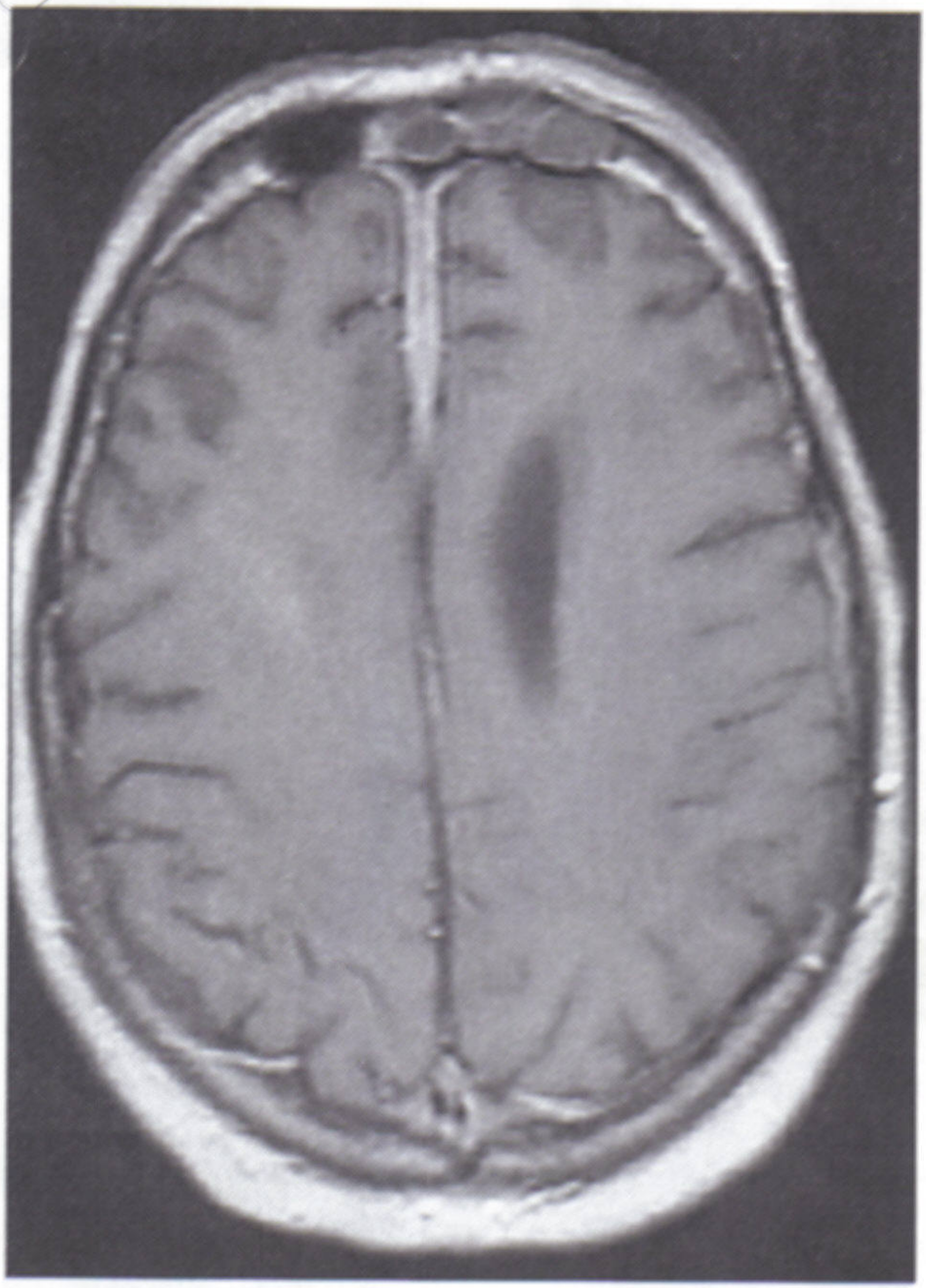
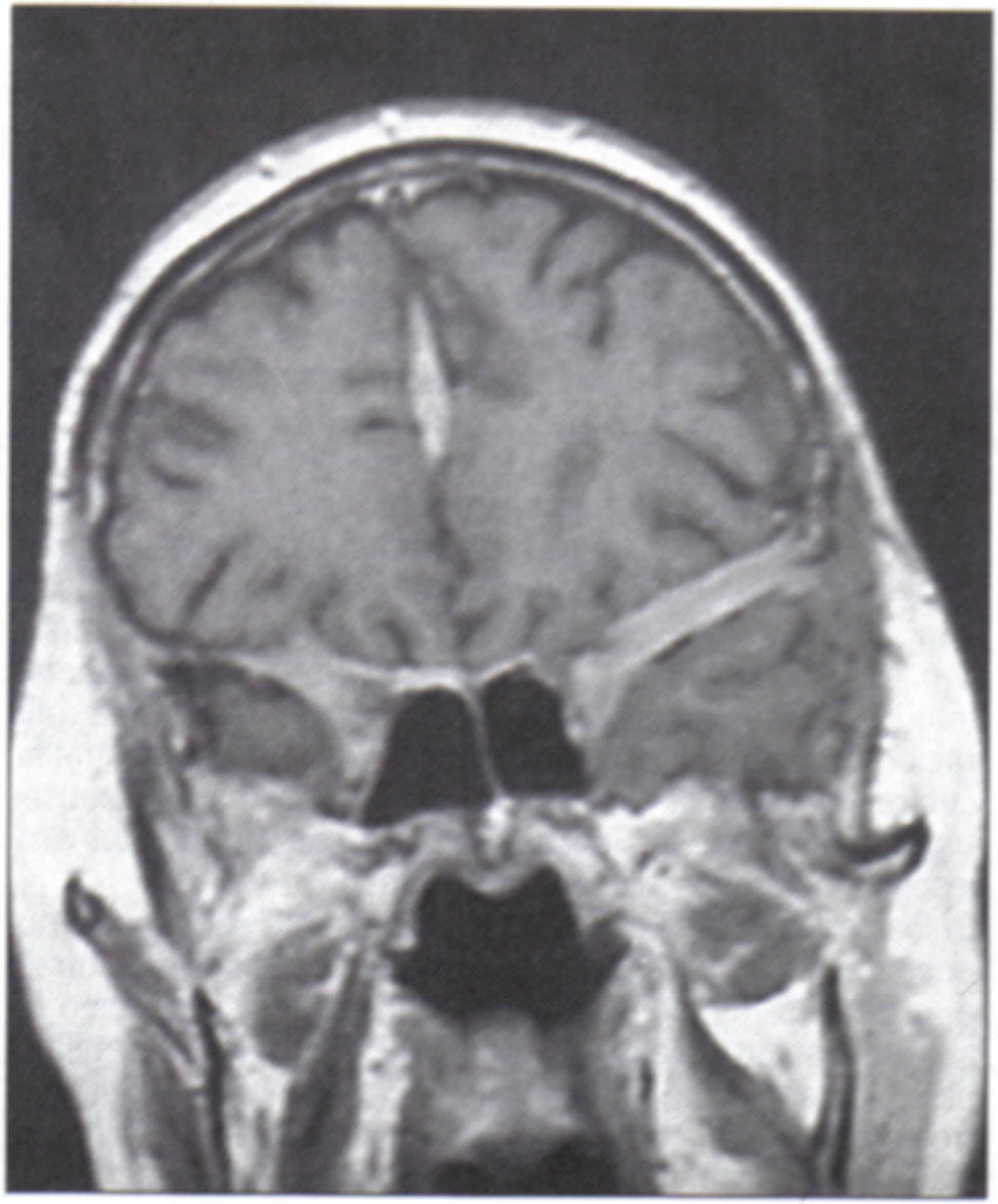
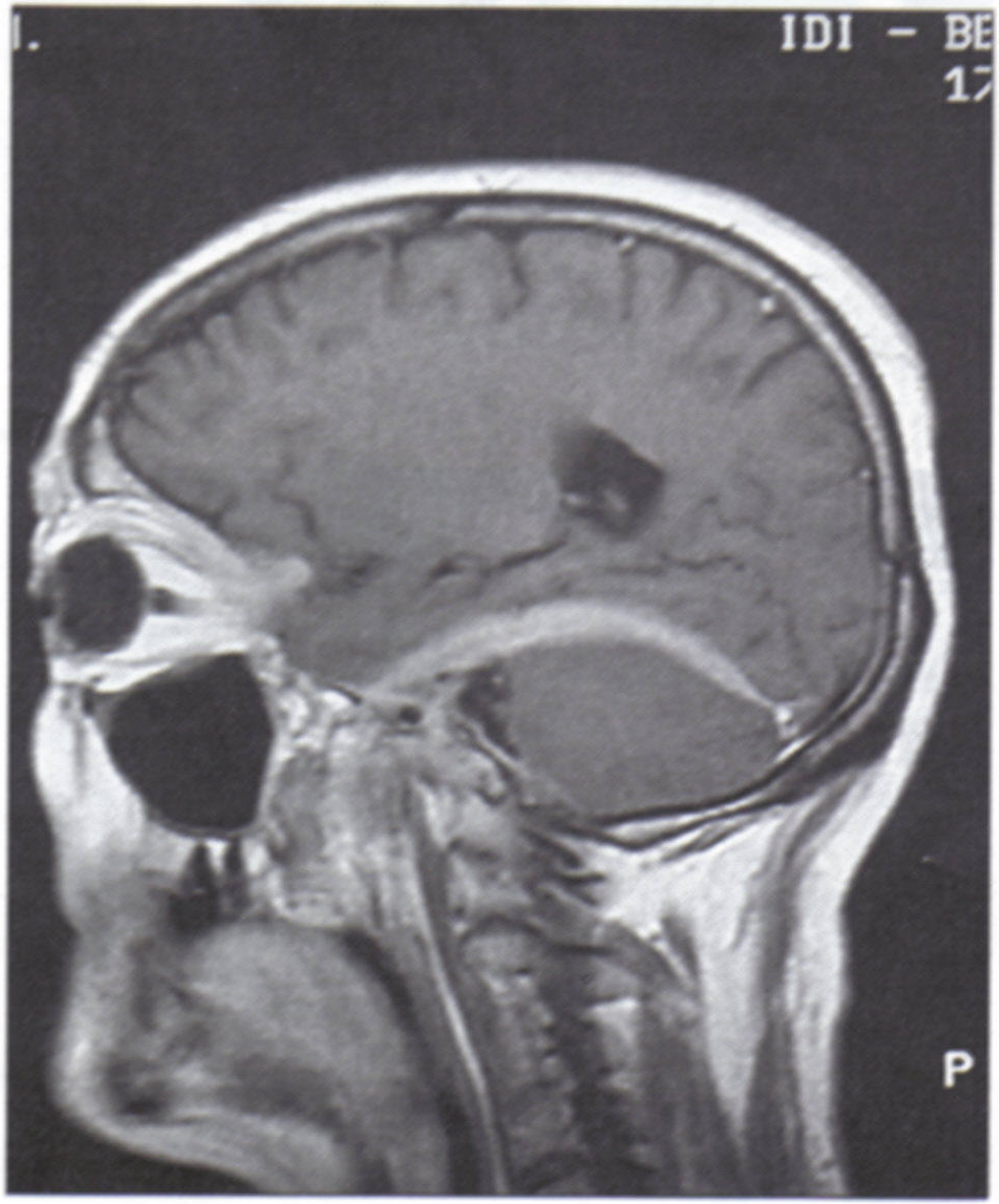


Fig. 6. RM craneal. Ocupación de la parte izquierda del seno frontal.





Figs. 7 y 8. RM craneal. Cortes sagital (fig. 7) y coronal (fig. 8) en secuencia potenciada en T1 tras la administración de contraste intravenoso. Engrosamiento y captación de la duramadre que se extiende al conducto auditivo interno y al seno cavernoso.

Se practicó una prueba diagnóstica

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O.D. Multineuritis craneal, una vez han abandonado el tronco del encéfalo.

Nervios afectos son:

- Ambos nervios ópticos
- Nervios faciales
- Afectación del VIII

Paciente de 49 a. sin A.P. de interés, que presenta meningitis crónica linfocitaria, con multineuropatía y paquimeningitis.

O.D. Meningitis infecciosas crónicas
Meningitis Neoplásicas
Meningitis inflamatorias

INFECCIOSAS:

- NEUROBRUCELOSIS
- ENFERMEDAD DE LYME
- TUBERCULOSIS
- MENINGITIS POR HONGOS
- NEUROLUES

MENINGITIS NEOPLÁSICAS:

- CARCINOMATOSAS
  Supervivencia 3-4 meses
- LINFOMA NO HODGKINIRIANOS
- GRANULOMATOSIS LINFOMATOIDE

SARCOIDOSIS: Afectación neurológica 5%.

Paquimeningitis (frecuente en Sarcoidosis)

PAQUIMENINGITIS CRANEAL: Hipertrófica idiopática

INFLAMATORIAS

Biopsia de órbita

GRANULOMATOSIS DE WEGENER

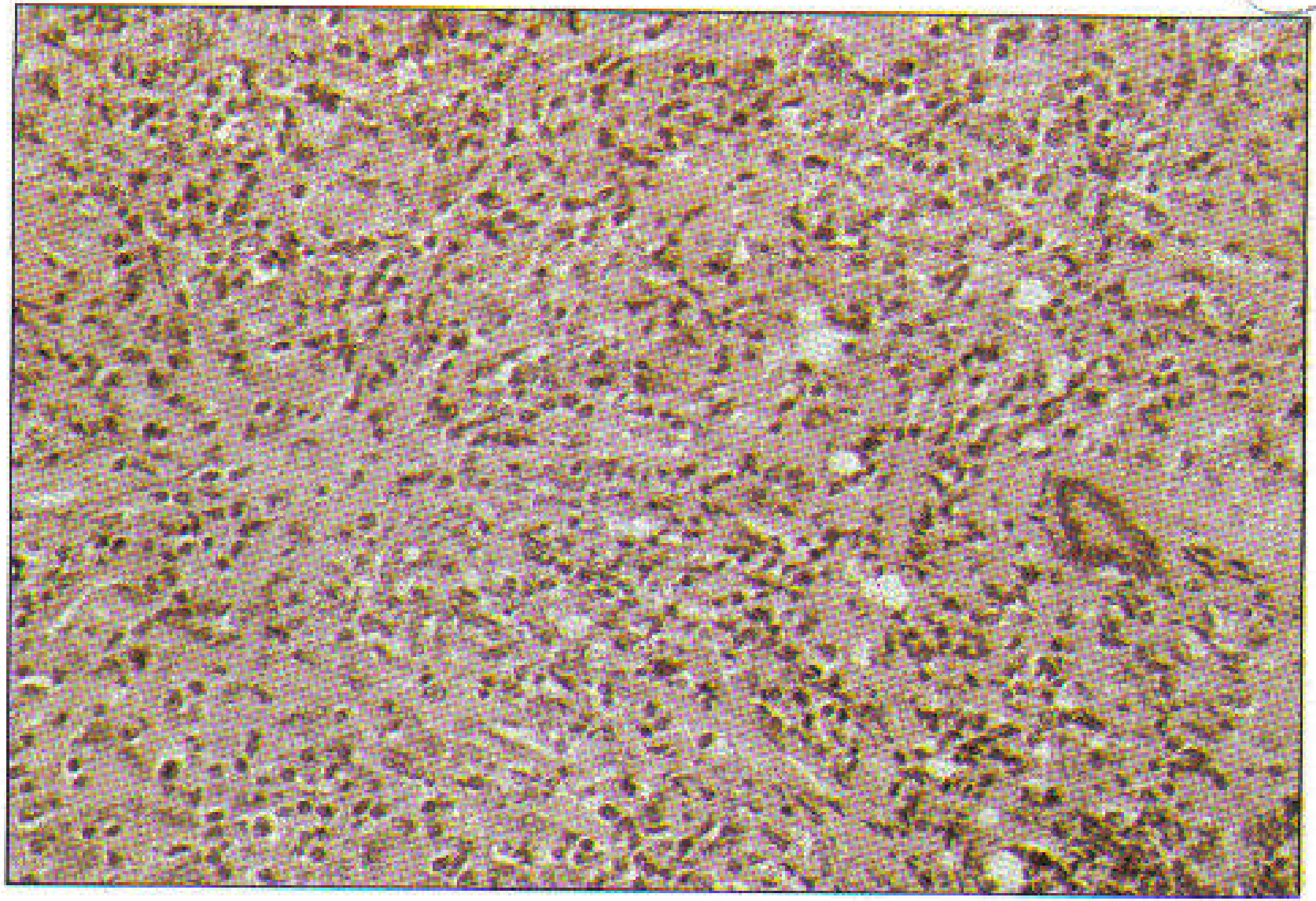


Fig. 9. Biopsia de tejido orbitario, en la que la que se observa sustitución del tejido adiposo por inflamación granulomatosa mixta con células gigantes multinucleadas (HE, ×200).

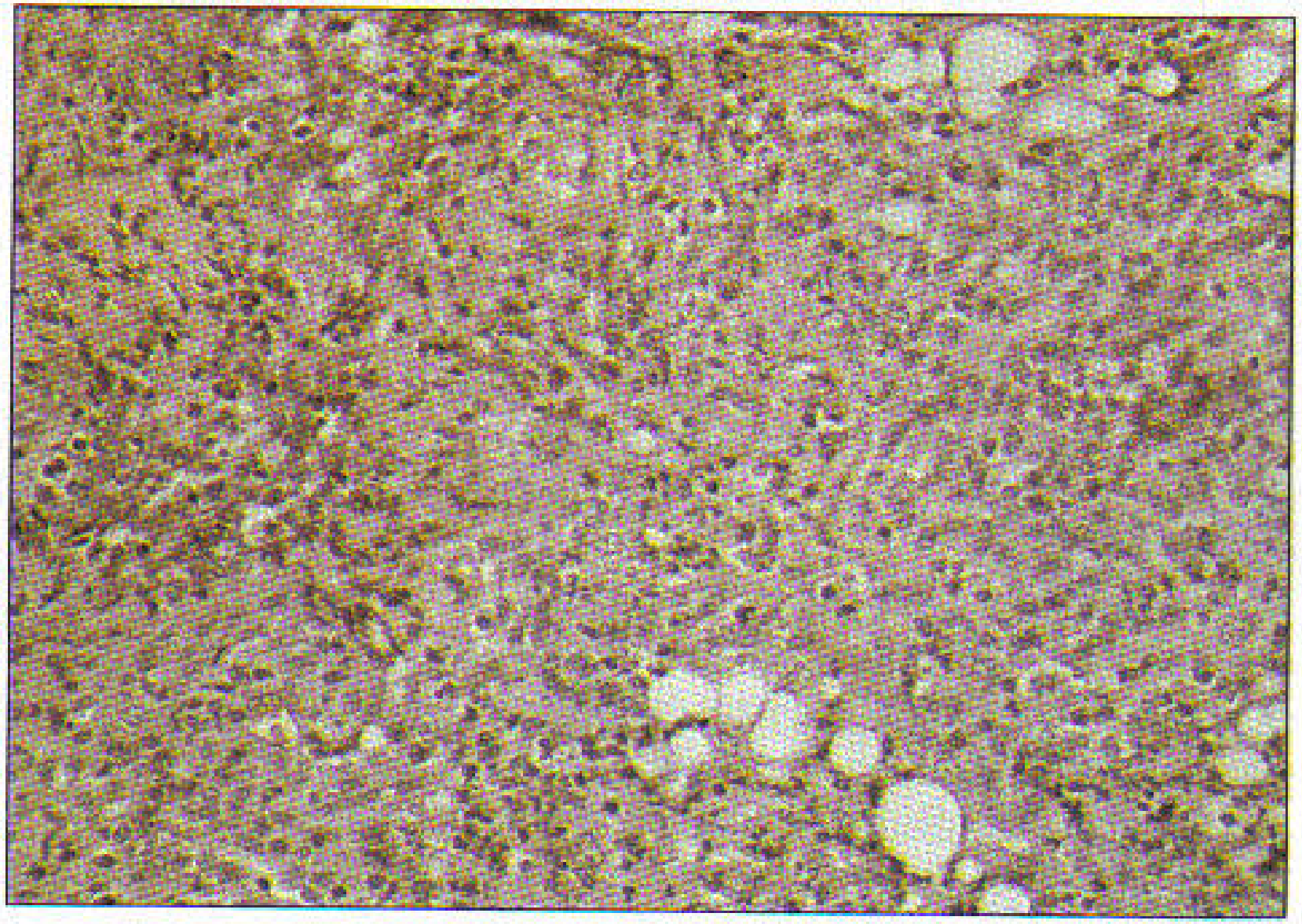


Fig. 10. Histiocitos epitelioides agrupados, formando un granuloma mal delimitado, adyacente a una zona de necrosis basófila, que contiene restos de polimorfonucleares neutrófilos (HE, ×200).

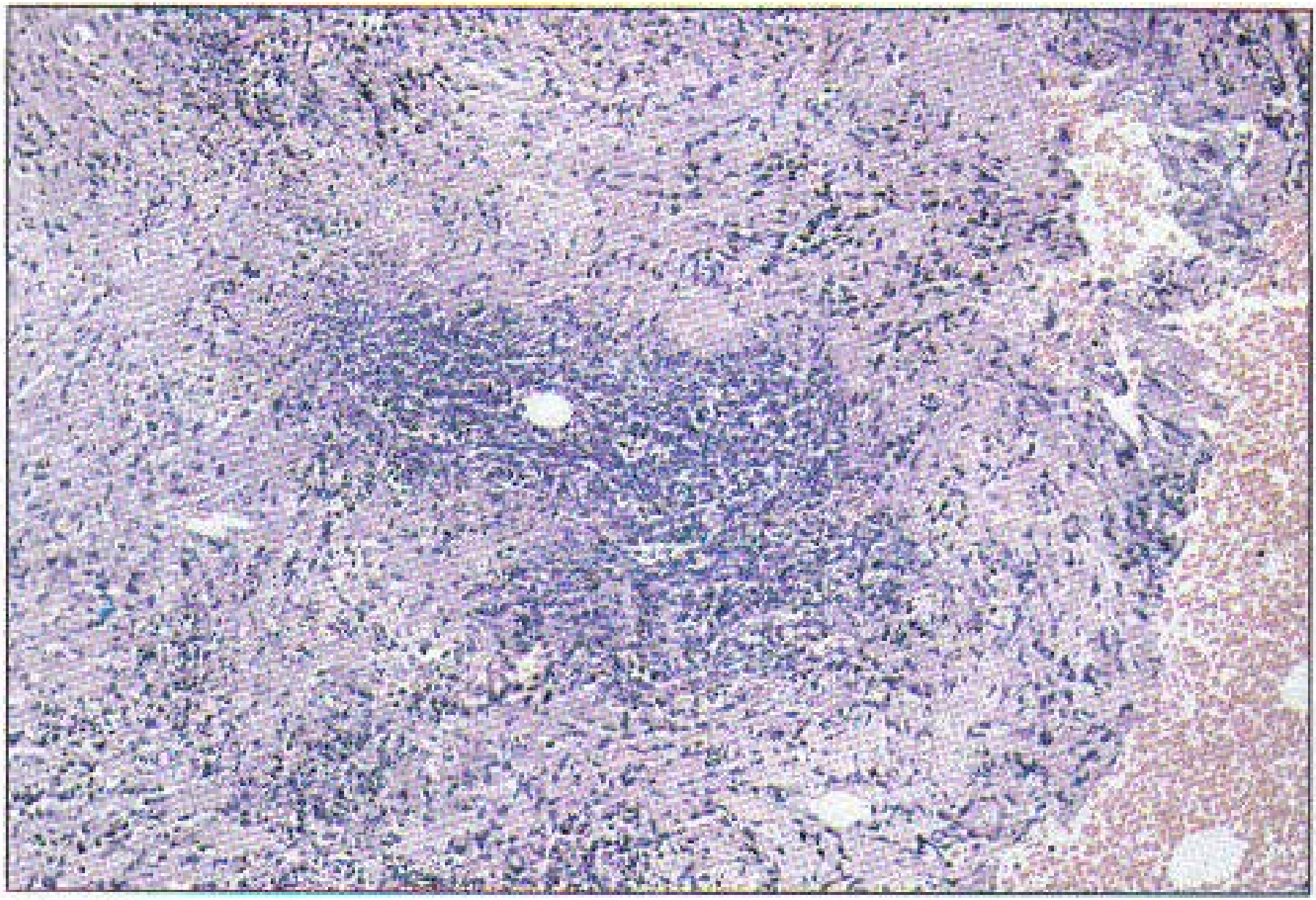


Fig. 11. Focos de necrosis extravascular de coloración basófila, aspecto granular y márgenes geográficos (HE, x200)

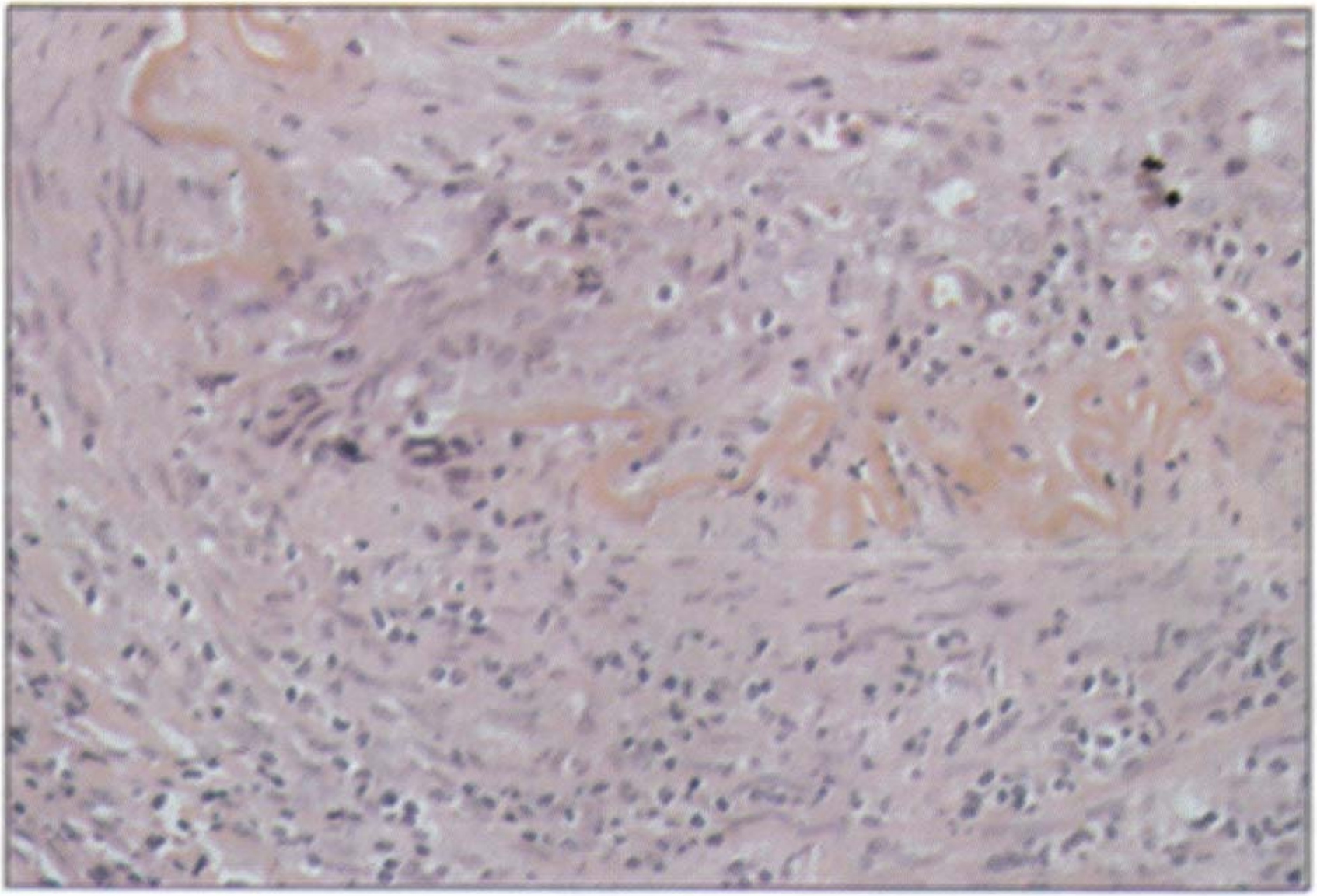


Fig. 12. Vasculitis en arteria de mediano calibre con fragmentación de fibras elásticas y oclusión de la luz vascular por un trombo recanalizado (HE, ×400).

FISIOPATOLOGÍA: de la afectación ocular, SNC en la vasculitis de Wegener.

- Ocular:
  - Afectación por contiguidad o extensión desde los senos paranasales. Seudo Tumor orbitario
  - Vasculitis focal Vasculitis retiniana.
- Sistema Nervioso más frecuente el SN periférico (35%)
- SNC:
  - Extensión por contiguidad
  - Formación de granulomas a distancia
  - Vasculitis

La infiltración granulomatosa de las meninges es muy poco frecuente clínicamente; aunque en las series de necros, existe afectación alrededor del 77%.

Neurological Involvement in Wegener's Granulomatosis: An Analysis of 324 Consecutive Patients at the Mayo Clinic

Hiroshi Nishino, MD,* Frank A. Rubino, MD,§ Richard A. DeRemee, MD,†
Jerry W. Swanson, MD,* and Joseph E. Parisi, MD‡

Neurological involvement in Wegener's granulomatosis was studied by reviewing the charts of 324 consecutive patients in whom the diagnosis was made at the Mayo Clinic. One hundred nine patients (33.6%) had neurological involvement. Peripheral neuropathy occurred in 53; cranial neuropathy, in 21; external ophthalmoplegia, in 16; cerebrovascular events, in 13; seizures, in 10; cerebritis, in 5; and miscellaneous involvement, in 25. The mean age and sex ratio were similar in the patients with and those without neurological involvement. Among the patients with peripheral neuropathy, 42 had mononeuropathy multiplex; 6, distal symmetrical polyneuropathy; and 5, unclassified peripheral neuropathy. Multiple mononeuropathy was a major presenting symptom in 8 patients. A significantly higher percentage of patients with peripheral neuropathy, compared to those without peripheral neuropathy, had kidney involvement ($p < 0.001$). The second, sixth, and seventh cranial nerves were most frequently affected. Multiple cranial nerves were affected in 8 patients. Unusual neurological manifestations in the miscellaneous group were spastic paraparesis, temporal arteritis, Horner's syndrome, and papilledema.

Nishino H, Rubino FA, DeRemee RA, Swanson JW, Parisi JE. Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. Ann Neurol 1993;33:4–9

Central Nervous System Involvement in Wegener Granulomatosis

Raphaèle Seror, MD, Alfred Mahr, MD, Jacky Ramanoelina, MD, Christian Pagnoux, MD, Pascal Cohen, MD, and Loïc Guillevin, MD

Abstract: Wegener granulomatosis (WG) is an antineutrophil cytoplasmic antibody (ANCA)-associated granulomatous vasculitis of small and medium-sized vessels. This vasculitis involves mainly the upper and lower respiratory tracts and kidneys, although WG may affect any organ. Central nervous system (CNS) involvement is an uncommon manifestation of WG, reported in 7%–11% of patients. Three major mechanisms have been incriminated as causing CNS disease in WG: contiguous invasion of granuloma from extracranial sites, remote intracranial granuloma, and CNS vasculitis. Herein we describe 6 patients with WG-related CNS involvement, 2 of whom had chronic hypertrophic pachymeningitis, 3 with pituitary involvement, and 1 with cerebral vasculitis. CNS involvement was present at disease onset in 2 patients and occurred 5–18 years after WG diagnosis in the remaining 4. Based on these observations and a review of the literature, we discuss the pathogenic mechanisms, clinical features, imaging findings, treatment, and outcome of meningeal, pituitary, and vascular involvement, with an emphasis on differential diagnoses, prognosis, and therapeutic management of WG-related CNS involvement.

(*Medicine* 2006;85:54–65)

in about 90% of patients, strongly suggests an autoimmune mechanism. Initially described as a combination of ear, nose, and throat (ENT), lower airway disease, and pauci-immune extracapillary glomerulonephritis, WG is now recognized as a highly polymorphous, multisystemic disorder that also frequently affects joints, skin, eyes, and virtually any tissue or organ.

Neurologic involvement is not uncommon in WG, with reported frequencies ranging from 22% to 54% of patients[3,20,21,23,36,63,74,94]. In most instances, neurologic signs reflect peripheral disease, whereas WG-related central nervous system (CNS) involvement is much rarer[3,20,21,23,36,63,74,94]. According to previous studies, CNS involvement was observed in 7%–11% of WG patients[20,21,36,63,74,94]. Slightly higher CNS-involvement rates of 8%–18%[3,23,36] were found when isolated cranial nerve palsies were also included in the spectrum of CNS symptoms.

To increase clinicians' awareness of this manifestation, we describe in detail 6 patients with WG-related CNS involvement and review the literature on this topic.

TABLE 1. Main Characteristics of 6 Patients With WG-Related CNS Involvement

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Male	Male	Female	Female	Male	Male
Prior WG history						
Age at 1st symptoms, yr	46	24	45	26	39	34
Age at diagnosis, yr	51	24	45	28	57	35
Organ involvement	ENT, lung, joints, PNS	ENT, lung, eye, cranial nerve V	ENT, eye, skin, joints	ENT, kidney, eye, joints	Lung, eye, joints, PNS, CNS, large vessels	None
Histologic proof (site)	No	Yes (ENT)	Yes (ENT)	Yes (ENT)	Yes (Lung)	-
ANCA status (IIF/ELISA)	P-ANCA, no specificity	C-ANCA, anti-PR3	C-ANCA, no specificity	C-ANCA, anti-PR3	C-ANCA, anti-PR3	-
WG-related CNS disease						
Delay after WG onset, yr	8	18	5	15	18 (0)*	0
Ongoing treatment	None	CS + MTX, then CS + IVIg	CS + oral CYC	CS + AZA + IVIg	CS + IV CYC + CMX	None
Clinical symptom	Headache	Headache, dysarthria, dysesthesia, seizures	Amenorrhea, galactorrhea	Polyuria, polydipsia	Polyuria, polydipsia	Headache, coma, nystagmus,cerebellar syndrome, cranial nerve VI palsy, intracranial hypertension
Pattern of CNS involvement	CHP	CHP	PG involvement	PG involvement	PG involvement	CNS vasculitis
Associated organ involvement	ENT, lung	None	ENT, eye	None	Lung	Lung†

ANCA status (IIF/ELISA)	P-ANCA/ anti-MPO	C-ANCA/ anti-PR3	C-ANCA/ anti-PR3	C-ANCA/ no specificity	Negative	Negative
ESR, mm /1st h	16	10	32	20	8	36
CSF examination	ND	Normal	Normal	ND	ND	Pleocytosis, elevated protein level
Pituitary-hormone status	ND	ND	Hyperprolactinemia (3N), panhypopituitarism	Hyperprolactinemia (1.5 N)	Hyperprolactinemia (1.5 N), panhypopituitarism	ND
WDT results	ND	ND	Central DI	Central DI	Central DI	ND
Cerebral imaging	Pachymeningitis of falx cerebri and tentorium cerebelli, hydrocephalus	Diffuse pachymeningitis	PG enlargement and enhancement	Nodular enlargment and enhancement of PG	Necrosis and nodular infiltration of the PG	Cerebellar hematoma, hydrocephalus
Specific therapy	IV CYC + oral CS	IV then oral CS + IV CYC, then MMF, then infliximab/ etanercept,then alemtuzumab	Infliximab + AZA	Oral CS + infliximab then MTX, reinitiation of infliximab	15-deoxyspergualin, then oral CS + IV CYC	Oral CS + IV CYC, then anti-tuberculosis therapy, then oral CS + IV CYC
Hormone-replacement therapy	None	None	None	Vasopressin	Vasopressin + L-thyroxine	None
Follow-up, mo	36	44	35	18	44	29
Clinical neurologic outcome	Remission	Remission, then death	Remission	Remission	Remission	Remission
Neurologic imaging outcome	Persistent abnormalities	Persistent abnormalities	Persistent abnormalities	NR	Normalization	Persistent abnormalities

Abbreviations: AZA = azathioprine; CHP = chronic hypertrophic pachymeningitis; CMX = co-trimoxazole; CS = corticosteroids; CSF = cerebrospinal fluid; CYC = cyclophosphamide; DI = diabetes insipidus; ELISA = enzyme-linked immunosorbent assay; ENT = ear, nose, and throat; ESR = erythrocyte sedimentation rate; IIF = indirect immunofluorescence assay; IVIg = intravenous immunoglobulins; MMF = mycophenolate mofetil; MPO = myeloperoxidase; MTX = methotrexate; N = normal values; ND = not done; NR = not reported; PG = pituitary gland; PNS = peripheral nervous system; PR3 = proteinase 3; WDT = water deprivation testing.

*Retrospectively considered to be the first sign of CNS vasculitis.

†Lung involvement, confirmed histologically and radiographically, appeared 6 months after CNS, which was considered the first symptom of WG.

TABLE 2. Frequency and Pattern of Neurologic Manifestations in WG, Previous and Present Reports

	First Author (Reference)								
Parameter	**Walton (94)**	**Drachman (21)**	**Anderson (3)**	**Fauci (23)**	**Hoffman (36)**	**Nishino (63)**	**Reinhold-Keller (74)**	**de Groot (20)**	**Present Report**
Year of publication	1958	1963	1975	1983	1992	1993	2000	2001	2006
Study design	Literature review	Literature review	Literature review	Prospective cohort	Prospective cohort	Retrospective cohort	Prospective cohort	Prospective cohort	Retrospective cohort
Total no. of patients	56	104	249	85	158	324	155	128	80
Neurologic involvement, n (%)	NR	56 (54)	64 (26)	19 (22)	NR	109 (34)	NR	64 (50)	23 (29)
Pattern of neurologic involvement									
PNS, n (%)	16 (29)	22 (21)	27 (11)	9 (11)	NR (15)	53 (16)	NR (40)	56 (44)	17 (21)
CNS, n (%)	4 (7)	NR	44 (18)*	10 (12)*	NR (8)*	5 (2)	NR (11)	9 (7)	6 (8)
Cranial neuropathy, n (%)	NR	12 (12)	Yes	8 (9)	Yes	21 (6)	NR	6 (5)	2 (3)
Pattern of CNS disease									
CHP, n (%)	NR	7 (7)	Yes	0	0	2 (0.6)	NR	1 (0.7)	3 (4)
PG involvement, n (%)	NR	4 (4)	Yes	1 (1)	1 (0.6)	1 (0.3)	NR	0	2 (3)
CNS vasculitis, n (%)	NR	Yes	12 (5)	NR	Yes	Yes	NR	Yes	2 (3)
Arterial/venous thrombosis, n (%)	NR	4 (4)	Yes	0	Yes	12 (4)	NR	NR	1 (1)
Intracerebral or subarachnoid hemorrhage, n (%)	NR	5 (5)	Yes	0	0	1 (0.3)	NR	NR	1 (1)
Seizures, n (%)	NR	NR	Yes	NR	NR	10 (3)	NR	NR	1 (1)
Miscellaneous, n (%)	NR	8 (8)	Yes	1 (1)	NR	33 (10)	NR	NR	0

Abbreviations: CHP = cranial hypertrophic pachymeningitis; CNS = central nervous system; NR = not reported; PG = pituitary gland; PNS = peripheral nervous system; Yes = present but number not given.

*Including cranial nerve neuropathies.

In conclusion, WG-related CNS involvement manifests in polymorphous but now well-characterized clinical pictures. Its accurate diagnosis requires clinical, laboratory, imaging, and eventually biopsy findings, with cautious exclusion of etiologies not related to WG, particularly infection. Further investigation is warranted to assess better the potential prognostic impact of this uncommon feature and, perhaps, to define specific therapeutic strategies for WG-related CNS involvement.

ORIGINAL CONTRIBUTION

Standardized Neurologic Evaluations of 128 Patients With Wegener Granulomatosis

Kirsten de Groot, MD; Diego K. Schmidt, MD; Andreas C. Arlt, MD; Wolfgang L. Gross, MD; Eva Reinhold-Keller, MD

Objective: To assess the frequency and type of neurologic involvement in a cohort of patients with generalized Wegener granulomatosis (WG).

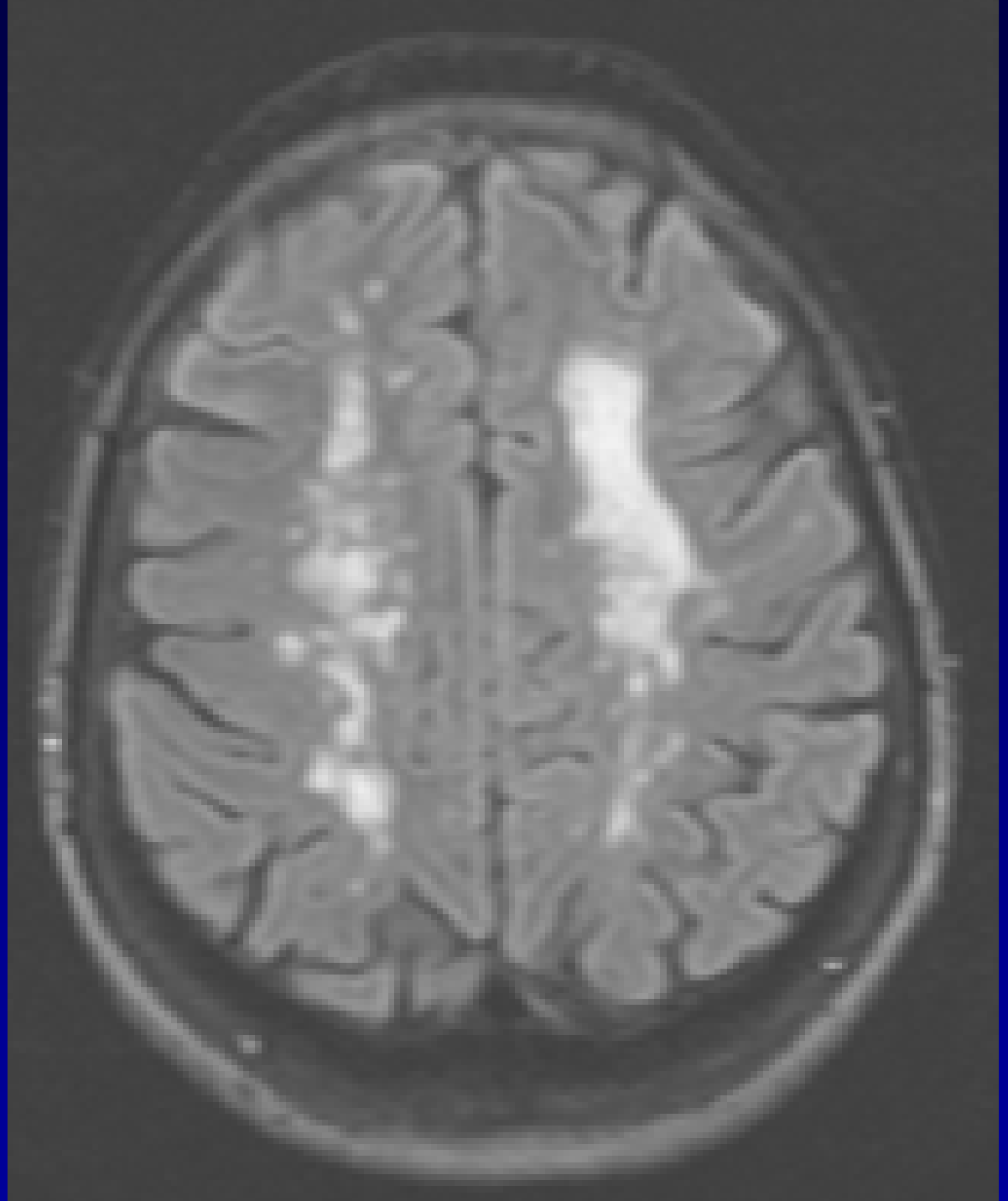
Patients and Methods: In a prospective analysis the clinical, electrophysiologic, radiological, and serologic data of 128 patients have been studied over a median observation period of 19 months (range, 1-60 months).

Results: Sixty-four patients (50%) revealed central or peripheral nervous system involvement. Peripheral neuropathy (PN) affected 56 patients, in 9 cases the central nervous system was involved, and in 6 cases the cranial nerves were involved. Thirty-one patients showed a distal symmetrical polyneuropathy, 25 a mononeuritis multiplex. Within the first 2 years of the disease course 47 of the 56 patients had developed their PN, sometimes as the initial symptom of WG. Patients with PN were significantly more often male (34 of 65 patients) than

female (22 of 63 patients, $P=.04$), were significantly older at the onset of WG (median age, 53 vs 44 years; $P=.001$), had a significantly larger disease extent ($P=.001$), and had higher classic antineutrophil cytoplasmic antibody titers ($P=.002$) than neurologically unaffected patients. Response to immunosuppression was moderate concerning peripheral nervous system manifestations.

Conclusions: Peripheral neuropathy is frequent in generalized WG, occurring early in the disease course. As PN can be the first and sole symptom of a beginning systemic vasculitis, it is important that in cases of PN of an unclear origin, interdisciplinary investigations are initiated to detect, treat, and closely follow-up a possible underlying WG, especially as these patients seem to have a more severe disease course.

Arch Neurol. 2001;58:1215-1221



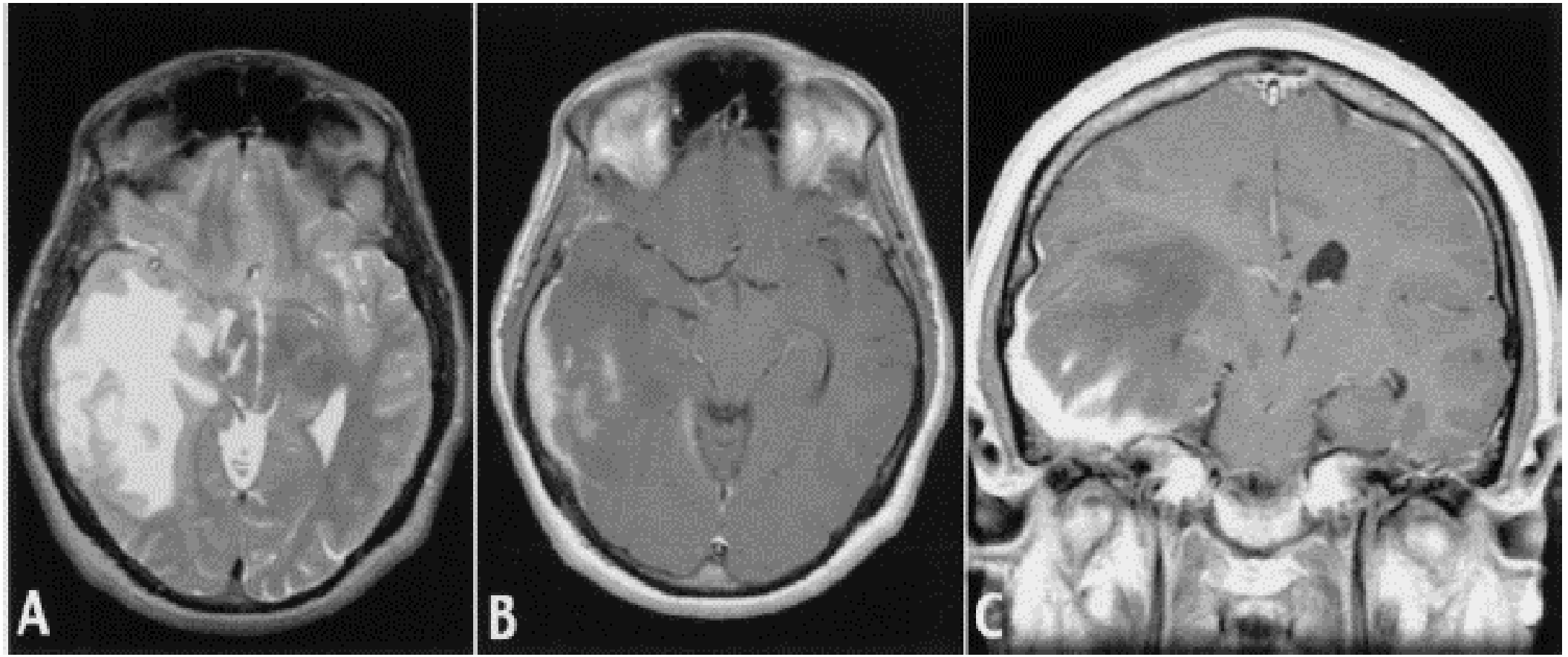


Figure 20. 41-year-old woman with central nervous system Wegener's granulomatosis. An axial *T*1 weighted image post intravenous gadolinium enhancement. Frontal sinus disease is shown (black arrow), and adjacent dural thickening is also present in the near and adjacent area (white arrow). Enhancing diffuse or focal dural thickening is the most common manifestation of cerebral Wegener's granulomatosis.

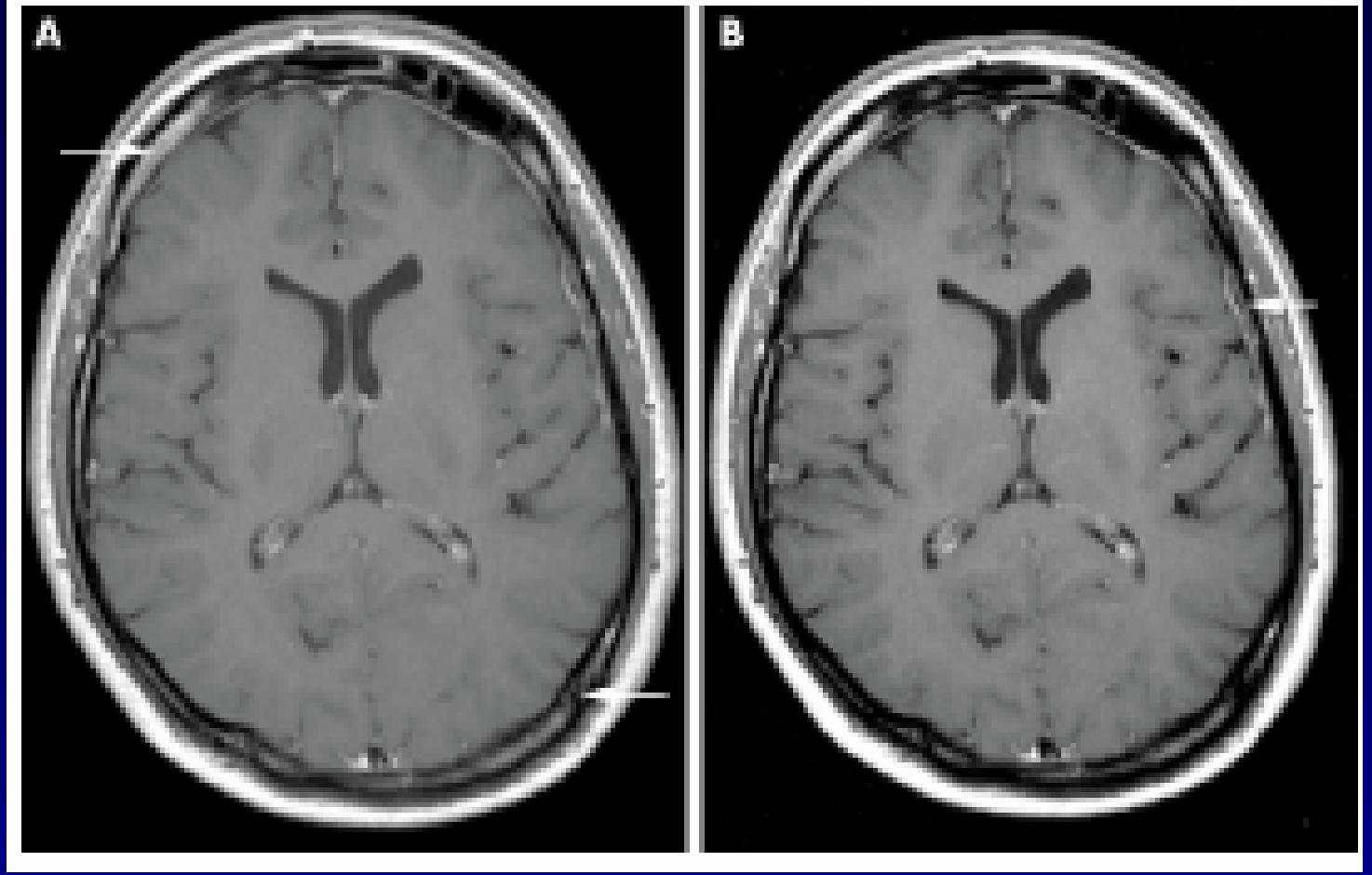


Figure 19. 57-year-old woman with central nervous system Wegener's granulomatosis. An axial fluid attenuated inversion recovery (FLAIR) image of the brain shows multiple areas of white matter signal hyperintensity. Although a non-specific finding, these appearances are a common form of cerebral Wegener's granulomatosis, indicative of vasculitis.