

# Inflammatory Pseudotumors of the Central Nervous System: Report of 3 Cases and a Literature Review

MARTIN HÄUSLER, MD, LARS SCHAADE, MD,  
VINCENT T. RAMAEKERS, MD, MARTIN DOENGES, MD,  
GERHARD HEIMANN, AND BERND SELLHAUS, MD

Inflammatory pseudotumors (IPs), mostly benign lesions characterized by fibrotic ground tissue and polyclonal mononuclear infiltrate, may affect all organ systems. IPs originating in the central nervous system (IP-CNS) are very rare, and their distinct histopathologic features are poorly characterized. Three otherwise healthy patients (age 8, 15, and 17 years) presented with focal neurologic symptoms (seizures,  $n = 2$ ; headaches,  $n = 1$ ), corresponding to a left temporal, left occipital, and left frontal IP, respectively, extending from meningeal structures into brain tissue. After resection, no recurrence was observed in patient 1 during 5 years of follow-up, whereas patient 2 developed a rapidly progressive local recurrence and a second intracerebral lesion despite antiviral, immunosuppressive, antibiotic, and radiation therapy. In patient 3, who also showed local recurrences, sequential histopathologic investigations revealed transformation to a semimalignant fibrohistiocytic tumor. In this patient, anaplastic lymphoma kinase (ALK) expression was also positive, whereas it was negative in patient 1. A detailed literature analysis confirmed that most IP-CNS arise from dural/meningeal structures ( $n = 34$ ). Intraparenchymatous ( $n = 7$ ), mixed intraparenchymatous/meningeal ( $n = 4$ ), and intraventricular lesions ( $n = 7$ ) or IP extend-

ing per continuitatem from intracerebral to extracerebral sites ( $n = 5$ ) were rare. The recurrence rate was 40% within 2 years in general. It was increased after incomplete resection and in female patients (multivariate Cox regression model,  $P < 0.02$ ). Although rare, IP-CNS are important differential diagnoses among tumor-like intracranial lesions. Their potential risk of malignant transformation and high risk of recurrence necessitate close follow-up, especially when resection is incomplete. Prospective multicenter trials are needed to optimize classification and treatment of this rare inflammatory lesion. HUM PATHOL 34:253-262. Copyright 2003, Elsevier Inc. All rights reserved.

**Key words:** inflammatory pseudotumor, brain neoplasm, inflammatory disease.

**Abbreviations:** ALK, anaplastic lymphoma kinase; CNS, central nervous system; IP, inflammatory pseudotumor; TCR, T-cell receptor; EBV, Epstein-Barr virus; PCR, polymerase chain reaction; CSF, cerebrospinal fluid MRI, magnetic resonance imaging; EMA, epithelial membrane antigen, SMA, smooth muscle antigen; LCA, leukocyte common antigen; VIM, vimentin; RR, relative risk.

Inflammatory pseudotumors (IPs), or inflammatory myofibroblastic tumors, represent a group of lesions that are histopathologically characterized by a collagenous stroma of different vascularization, spindle cells, and a polyclonal mononuclear infiltrate.<sup>1,2</sup> In contrast to the lung, mesentery, omentum, retroperitoneum, genitourinary tract, or upper respiratory tract,<sup>1-3</sup> IPs affecting primarily the central nervous system (IP-CNS) are very rare, with fewer than 60 reported cases. According to Tresser et al,<sup>4</sup> who reviewed the clinical features of 26 patients with IP-CNS described as of 1995, nonspecific complaints such as headaches, seizures, pareses, vision disturbance, and ataxia may be the most common symptoms.<sup>4</sup> From their data, these authors also calculated a recurrence rate of 12.5% when surgical resection was not followed by radiation therapy.<sup>4</sup>

Histopathologically, IPs show heterogeneous features, which explains the variety of synonymous expressions, including fibrous xanthoma, xanthomatous

pseudotumor, plasma cell granuloma, plasma cell/histiocytoma complex, pseudosarcomatous fibromixoid tumors, and inflammatory myofibrohistiocytic proliferation.<sup>5</sup> Nevertheless, major subgroups have been identified among IPs not affecting the CNS (IP-nCNS), including a predominant myxoid/vascular pattern resembling granulation tissue, a compact spindle cellular and a hypocellular fibrotic pattern in nonpulmonary IP-nCNS, and an organizing pneumonia pattern with central hyalinization, a fibrous histiocytoma-like pattern, and a lymphoplasmacytic pattern in pulmonary IP-nCNS.<sup>1,2</sup> Although basically considered benign lesions, IP-nCNS may invade vessels<sup>1,6</sup> or, very rarely, even undergo malign transformation.<sup>1,7</sup> In 2 pulmonary cases, for example, transformation to malignant fibrous histiocytomas was reported.<sup>7</sup> For IP-CNS, in contrast, a similar classification is not yet available.

In this report we focus on histopathologic characteristics of IP-CNS, on their intracranial growth patterns, and on the clinical outcomes. With reference to 3 new cases and a detailed literature analysis, we suggest that although it shares characteristics with IP-nCNS, IP-CNS may be a distinct disease entity that carries a high risk of local recurrence in cases of incomplete resection, and may undergo malign transformation.

## PATIENTS AND METHODS

Detailed clinical records were available for the 3 patients with IP-CNS who had been treated at the University Hospital

From the Department of Pediatrics; Institute of Medical Microbiology, Division of Virology; Department of Neuroradiology, and Institute of Neuropathology, University Hospital, RWTH Aachen, Germany. Accepted for publication November 21, 2002.

Address correspondence and reprint requests to M. Häusler, Department of Pediatrics, University Hospital, RWTH Aachen, Pauwelsstr. 30, 52074 Aachen, Germany.

Copyright 2003, Elsevier Inc. All rights reserved.  
0046-8177/03/3403-0009\$30.00/0  
doi:10.1053/hupa.2003.35

RWTH Aachen between 1996 and 2001. One patient was suffering from an additional pulmonary IP. To begin, 7- $\mu$ m-thick sections from formalin-fixed and paraffin-embedded tissue specimens were stained for hematoxylin and eosin and Elastica-van Gieson according to routine methods. Immunohistochemistry was also performed according to routine methods with peroxidase/DAB or alkaline phosphatase/RED. Antibodies were directed against leukocyte common antigen (LCA), B cells (CD20), T cells (CD45RO), kappa and lambda immunoglobulin chains, epithelial membrane antigen (EMA), vimentin (VIM), desmin, smooth muscle antigen (SMA), S-100 antigen, Ki67/MIBI, and anaplastic lymphoma kinase (ALK). All antibodies were purchased from Dako (Hamburg, Germany). Polymerase chain reaction (PCR) T-cell receptor (TCR) investigation for  $\gamma$  chain rearrangement was performed as reported previously.<sup>8</sup>

PCR investigation for the presence of viral genome was performed on cerebrospinal fluid (CSF) (patient 2) and paraffin-embedded brain (patients 1 and 3) or pulmonary tissue (patient 1). Nucleic acid was extracted from CSF using the QIAgen Blood Kit (Qiagen, Hilden, Germany) and from paraffin-embedded tissues with the QIAgen Tissue Kit. PCR for detection of Epstein-Barr virus (EBV) and human herpes virus type 6 and 8 DNA was performed according to previously published protocols.<sup>9</sup> PCR for detection of herpes simplex virus type 1 and 2 DNA (target, polymerase gene) and varicella zoster virus DNA (target, open reading frame [ORF] 29) was performed on a LightCycler instrument (Roche Biochemicals, Mannheim, Germany) applying the fluorescence resonance energy transfer technology with 2 fluorophore-labeled hybridization probes. Protocols have repeatedly passed national and international external quality control cycles. The detection limit was 1000 to 2000 genomes /mL of CSF or 200 to 400 genomes in brain tissue. Detection of JC virus DNA from CSF was performed by the Institute of Virology and Immunobiology, University of Würzburg a national reference laboratory for polyoma viruses. Evaluation of intrathecal synthesis of antibodies to neurotropic viruses was performed as described previously.<sup>10</sup>

The literature review was based on a PUB MED and WEB OF SCIENCE search for the key words "inflammatory pseudotumor", "plasma cell granuloma," "(inflammatory) myofibroblastic tumor," and further references cited in previously published articles. Reports on orbital pseudotumors extending into the cranial cavity were excluded, because they represent a well-described, distinct entity.<sup>11</sup> Publications on isolated pachymeningitis, lymphocyte-rich meningiomas, and cases positive for EMA expression indicative of meningiomas were also excluded.

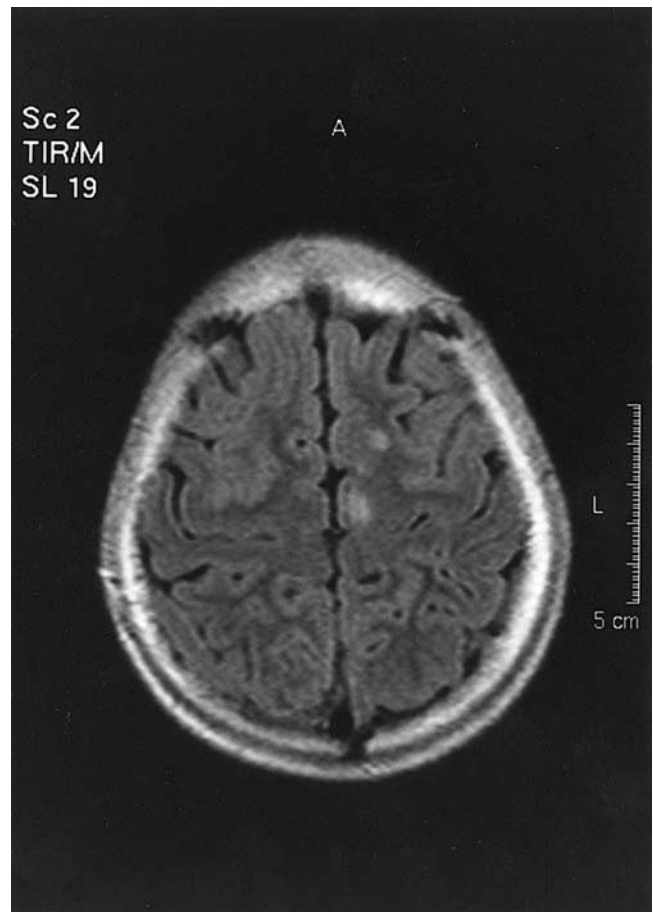
The relationship between distinct patient characteristics and tumor recurrence was analyzed using the Cox regression model.<sup>12</sup> The variables showing a significant relationship with recurrence on univariate analysis were included in a multivariate forward stepwise analysis to determine factors independently related to recurrence (probability of stepwise entry or removal, 0.05 and 0.1, respectively). Kaplan-Meier plots were constructed for the recurrence rate in general and for variables related with recurrence (log-rank statistics;  $P < 0.05$  considered significant). The Statistical Package for Social Sciences software was used for data analysis.

## RESULTS

### Patient Reports

#### Patient 1

In this boy, a left thoracic IP had necessitated left-sided pneumonectomy at age 2 years. Six years later

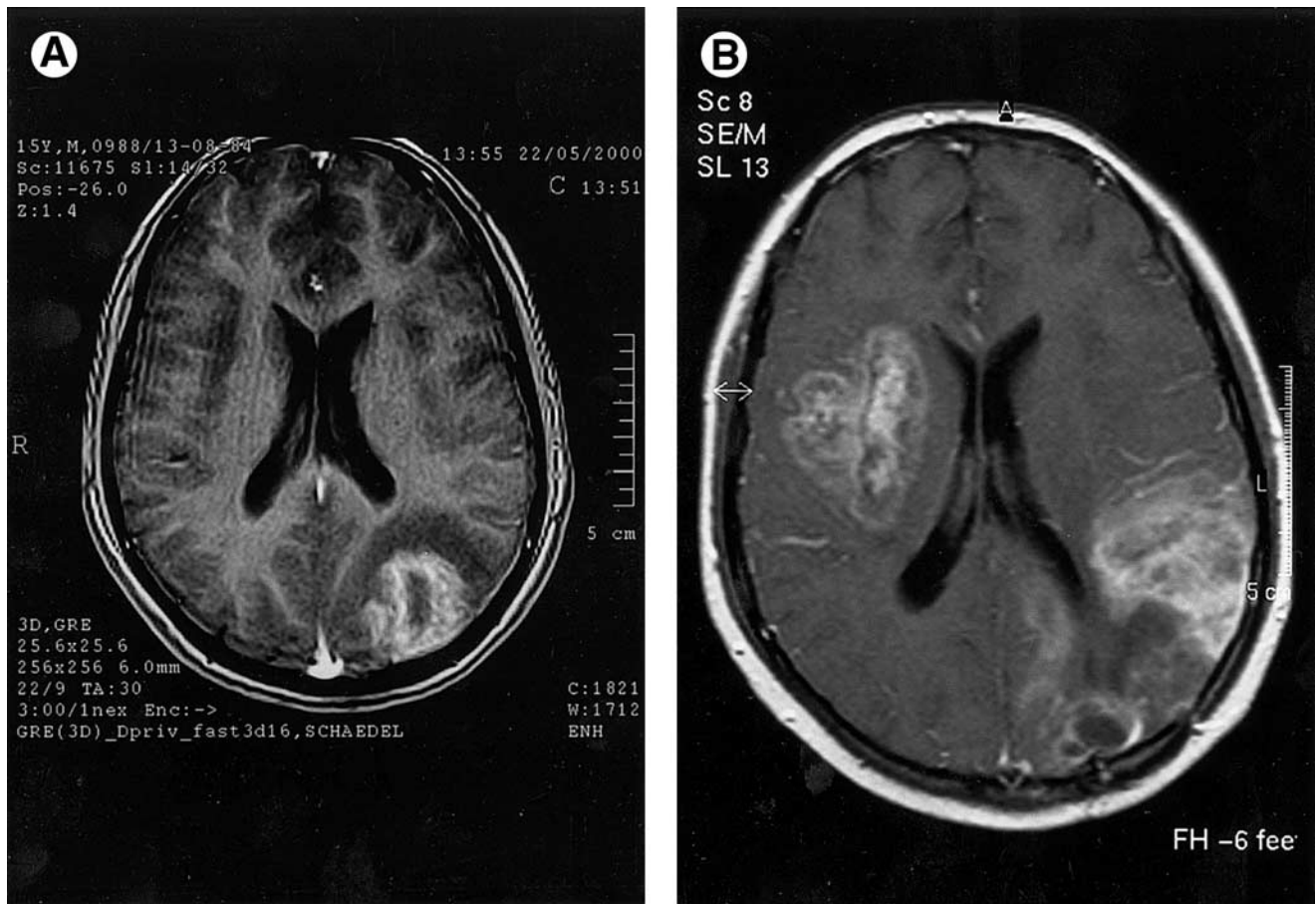


**FIGURE 1.** T2-weighted MRI image of patient 1, performed 4 years after resection of the temporal lesion, showing 2 subcortical residual signal intense lesions.

he suffered a right-sided seizure due to a round, calcified non-contrast-enhanced lesion within the left temporal lobe. During surgery, a solid, not well-delineated tumor infiltrating the surrounding brain tissue was found and resected incompletely. After surgery, no radiation or chemotherapy was performed. Postsurgical magnetic resonance imaging (MRI) revealed a small residual left temporal lesion and 2 left subcortical intraparenchymatous contrast-enhanced lesions without surrounding edema. Because of the neurotopography of the subcortical lesions and the good postsurgical seizure control, these lesions were not resected. During 5 years of follow-up, the brain lesions did not grow, the contrast medium uptake disappeared, and no pulmonary recurrence occurred (Fig 1). Clinically, the patient shows an attention deficiency disorder and a disturbed short-term memory. Laboratory tests for autoimmune and immunodeficiency disorders proved normal.

#### Patient 2

This 15-year-old male patient presented with a right-sided epileptic seizure, corresponding to a contrast-enhanced left occipital lesion (Fig 2A). During surgery, this lesion was found to infiltrate the brain, and



**FIGURE 2.** Patient 2. (A) T1-weighted, contrast-enhanced MRI image performed before surgery (T1-weighted), showing a large contrast-enhanced lesion with central necrosis and perifocal edema. (B), T1-weighted, contrast-enhanced MRI taken 6 months later showing extensive progressive brain destruction with an additional right hemispheric intracerebral lesion.

an incomplete resection was performed. Postsurgically, thoracic imaging, bone marrow, and microbiologic investigations were normal. CSF analysis revealed a selective intrathecal synthesis of IgG antibodies to herpes simplex virus but not to further neurotropic viruses. After surgery, the patient suffered persistent right-sided hemianopsia without further neurologic or cognitive deficits, and no additional treatment was initiated. A control brain MRI scan taken 2-1/2 months later showed a residual cystic structure within the former resection area, surrounded by a new contrast-enhanced inflammatory process now involving 1/3 of the left hemisphere and showing perifocal edema. Spinal lesions were absent. At that time, no more intrathecal anti-herpes simplex virus antibody synthesis was present. During the subsequent 2 months, progressive aphasia with recurrent focal seizures occurred, rapidly followed by right-sided hemiparesis and a stupor state. Simultaneously the lesion showed local progression that did not respond to steroid treatment, long-term acyclovir therapy, a 2-week virostatic course of zidovudine, cidofovin, and ribavirin as well as antibiotic treatment empirically performed in the course of steroid-related infectious complications (cefotiam, metronidazole, ciprofloxacin, and clindamycin). Six months

after the diagnosis, after local radiation with a total of 20 Gy in daily 2-Gy fractions, a new right-hemispheric lesion occurred (Fig 2B). At 1-1/2 years after manifestation, the patient showed spastic tetraparesis and unimproved mental status. Cranial computed tomography revealed extensive residual lesions with global brain atrophy, widening of inner CSF spaces, left-occipital porencephaly, and extensive calcifications within the areas of former inflammation. Repeated thoracic and abdominal imaging revealed normal findings, as did blood analysis for malign hematologic or autoimmune diseases.

### Patient 3

This 17-year-old female presented with left frontal headaches. A brain MRI scan revealed a large ( $6 \times 6 \times 3.5$  cm) left frontal lesion with perifocal edema, homogeneous gadolinium uptake, and an angiographically verified blood supply via the frontal meningeal and the superficial temporal arteries. At surgery, the lesion was found to be of fibrous consistency, attached to the hypervascularized dura, and extending into the white matter. According to macroscopic criteria, a complete resection was performed. Two years after primary sur-



gery, an asymptomatic 1 × 1 cm left-frontal intracerebral lesion adjacent to the former resection cavity was detected. Again, surgical resection was performed. Three years after the second operation, a new 1 × 1 cm left frontal local recurrence occurred that also necessitated resection. Repeated thoracic imaging ruled out pulmonary lesions.

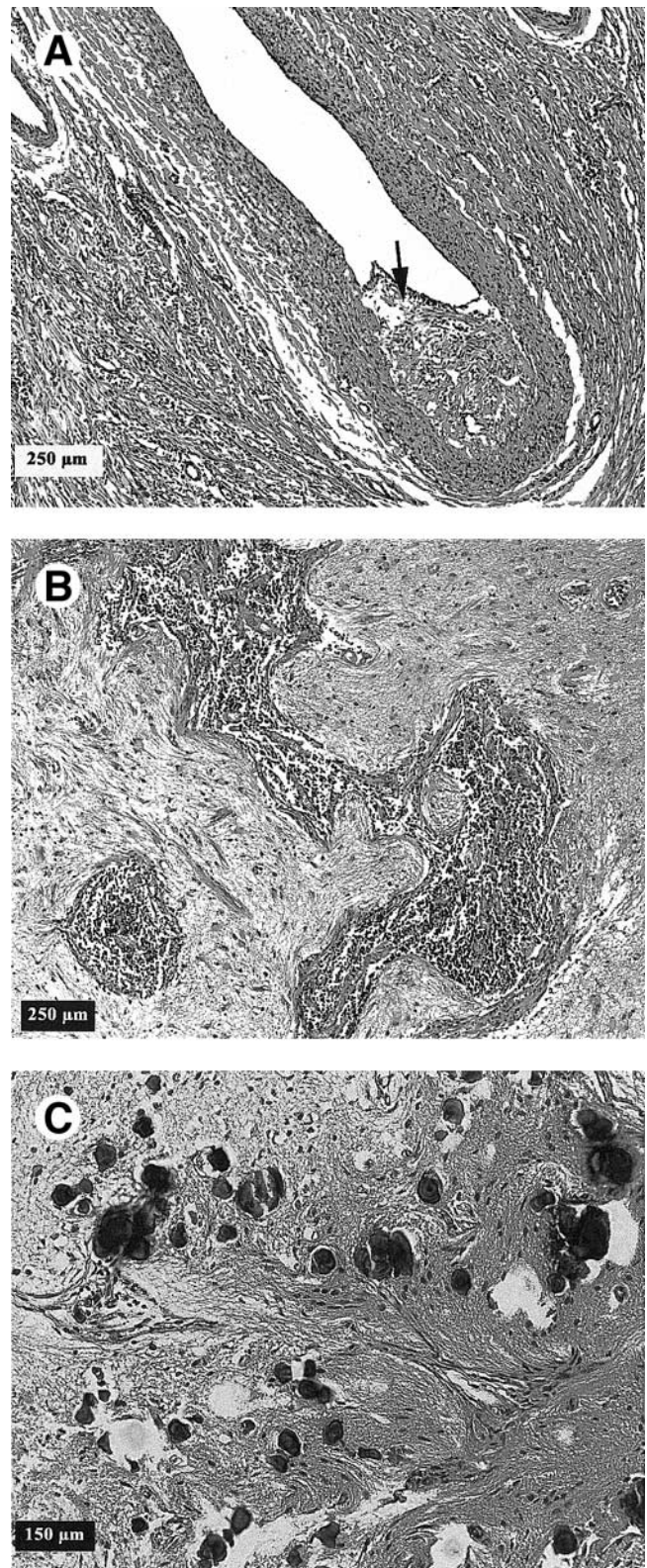
## Histopathologic Findings

### Patient 1

The circumscribed pulmonary lesion represented a highly vascularized inflammatory pseudotumor composed of spindle cells with collagenous stroma and a dense lymphoplasmacellular infiltrate. The spindle cells were arranged in a parallel fashion showing regular and normochromic nuclei (MIB-1 index, <1%). Immunohistochemically, they coexpressed VIM, SMA, and actin but were negative for desmin and ALK. The inflammatory cells were of polyclonal origin (T, B, and plasma cells) and scattered throughout the lesion, occasionally forming aggregates or showing perivascular accumulation. In some areas, lymphocytes were suspected to transigrate small vessel walls and intravascular IP tissue was detected within the lesion (Fig 3A). The superficial components of the brain mass consisted of thickened meninges with an accumulation of fibroblasts producing collagen fibers and a mononuclear infiltrate (B, T, and plasma cells), but no calcifications or germinal centers. Focally, mononuclear cells extended from the meninges along Virchow-Robin spaces into deeper brain structures, but without invading surrounding brain tissue (Fig 3B). At other sites, the superficial cortical brain structures adjacent to the inflammatory areas were penetrated by fibrotic septa, also arising from the meningeal lesion. Focally, the glioneuronal tissue adjacent to these septa contained psammomatous bodies, whereas inflammatory cells were not present (Fig 3C). Some of the small vessel walls showed circular fibrotic thickening. The MIB-1 index of the fibroblast population was <1%. The cerebral fibroblasts were negative for ALK expression and, in contrast to the pulmonary lesion, did not express actin or SMA either.

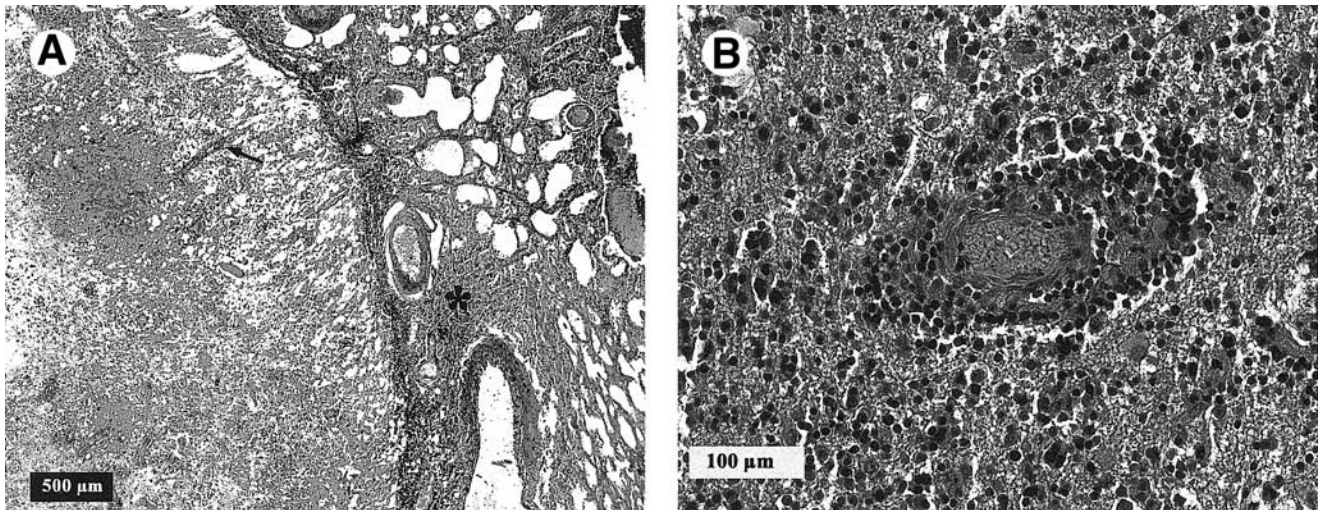
### Patient 2

Histopathology revealed thickened meninges due to multiple layers of collagenous bundles. Lymphoplasmocellular infiltrates were prominent, especially in inner meningeal layers and surrounding blood vessels. The superficial cortical structures were destroyed by extensive inflammation consisting of B and T lymphocytes, plasma cells, and macrophages. Germinal centers were not observed (Fig 4). The inflammatory cells extended within Virchow-Robin spaces from the inflamed meningeal structures into the adjacent cortex, from where lymphocytes diffusely infiltrated and destroyed surrounding brain tissue. Fibrotic thickening with a decreased intraluminal diameter was found in small meningeal veins. The MIB-1 index of the fibroblasts was

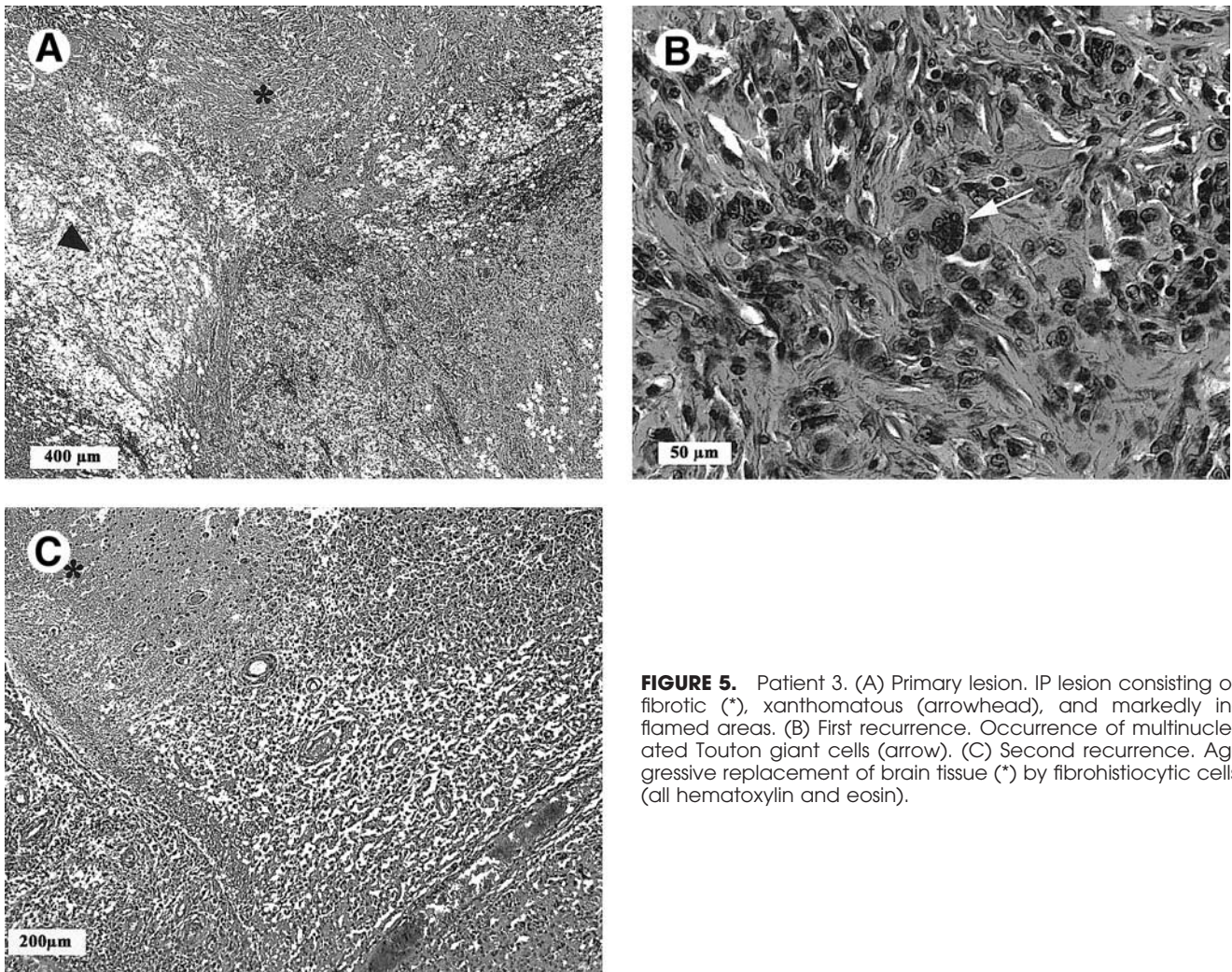


**FIGURE 3.** Patient 1, all hematoxylin and eosin. (A) Pulmonary venous vessel located within the IP lesion, showing intraluminal IP tissue (arrow). (B) Glioneuronal tissue penetrated by fibrovascular septa, containing a mononuclear infiltrate. The inflammatory cells are prominent around vessels but do not infiltrate brain tissue. (C) Numerous psammomatous bodies focally present in glioneuronal tissue adjacent to fibrotic septa.





**FIGURE 4.** Patient 2, all hematoxylin and eosin. (A) Extensively thickened and fibrotic meninges containing a marked mononuclear infiltrate(\*) that is most prominent adjacent to the brain surface. The infiltrate extends within Virchow-Robin spaces (arrow) and diffusely infiltrates brain tissue. Focal intraparenchymatous hemorrhages are present. (B) Extensive perivascular mononuclear inflammation extending into surrounding brain tissue.



**FIGURE 5.** Patient 3. (A) Primary lesion. IP lesion consisting of fibrotic (\*), xanthomatous (arrowhead), and markedly inflamed areas. (B) First recurrence. Occurrence of multinucleated Touton giant cells (arrow). (C) Second recurrence. Aggressive replacement of brain tissue (\*) by fibrohistiocytic cells (all hematoxylin and eosin).



<1%. PCR investigation of TCR-gamma chains revealed no monoclonal T cell proliferation.

### Patient 3

The findings in the first lesion (Fig 5A) were consistent with the diagnosis of an IP-CNS, again showing thickened fibrotic meninges and fibrohistiocytic areas admixed with infiltrated cerebral cortex. Scattered or focally aggregated mononuclear cells (B and T cells, plasma cells, and macrophages) and xanthomatous cells were found throughout the lesion, with the density highest within the meninges. Anaplastic elements or mitoses were absent, as were germinal centers and meningothelial differentiation of spindle cells. Few multinucleated cells were seen. Emperipolesis was absent. The first recurrence (Fig 5B) showed similar tissue components, but also contained focal accumulations of multinucleated cells with centrally arranged nuclei, resembling Touton giant cells. The nuclei of the fibrohistiocytic cells were more prominent, and mitoses were also found (MIB index, 1% to 3%). The adjacent cortical tissue was severely infiltrated and replaced by the tumor. Xanthomatous cells were abundant and indicative of tissue absorption. A fibrohistiocytic tumor with a high Touton giant cell component was suspected. The second recurrence (Fig 5C) still showed a marked polyclonal mononuclear infiltrate. The fibrohistiocytic tissue component (CD68 positive) had increased, however. It showed an increasing number of mitoses (MIB index, focally 10%) and aggressively destroyed brain tissue. Pleomorphic and multinucleated giant cells were abundant. A fibrohistiocytic tumor of low malignancy not otherwise specified (NOS) was now diagnosed. In the course of the disease, the fibrohistiocytic component became increasingly positive for VIM and SMA, whereas ALK expression was present from disease onset. Staining for S-100 antigen was positive in reactive astroglial cells but negative in the fibrohistiocytes.

In all patients, stains for mycobacterial, bacterial, and fungal diseases proved negative. No morphological signs of viral diseases, such as inclusion bodies, were found. Immunohistochemistry ruled out EMA expression on spindle cells. The staining for kappa and lambda chains revealed polyclonal B cell infiltrates.

### PCR Investigations

PCR investigations failed to detect viral DNA from EBV, herpes simplex virus, or type 6 and 8 human herpes viruses in paraffin-embedded brain and pulmonary tissue of patient 1 or in brain tissue of patients 1 and 3. In patient 2, CSF PCR proved negative for mycobacteria, herpes simplex virus, varicella zoster virus, JC virus, EBV, and type 6 and type 8 human herpesviruses.

### Review of the Literature

A list of the works reviewed is available from the authors on request.

### Intracranial Localization of the Brain Lesions

According to the anatomical distribution, 5 groups of lesions could be identified: (A) intraparenchymatous lesions ( $n = 7$ ); (B) meningeal lesions ( $n = 34$ ; including 7 with hypophyseal/hypothalamic dysfunction due to compression of diencephalic structures and 13 with infiltration of brain tissue); (C) mixed intraparenchymatous and meningeal lesions ( $n = 4$ ); (D) intraventricular lesions ( $n = 7$ , in 5 presumably deriving from the choroid plexus); and (E) IP continuously extending between the cranial cavity and the sphenoidal sinus ( $n = 2$ ), right temporal muscle ( $n = 1$ ), pterygopalatine fossa ( $n = 1$ ), or right nasal cavity ( $n = 1$ ). Additional pulmonary IPs were present in 6 cases, presenting either before ( $n = 3$ ) or simultaneously with ( $n = 3$ ) the CNS manifestations.

### Histopathologic Findings

The most frequent ground tissue pattern reported in the literature resembled the compact spindle cellular or hypocellular fibrotic pattern of nonpulmonary IP-nCNS, containing a mononuclear infiltrate dominated by plasma cells<sup>1</sup> (Table 1). In 8 other patients, a hyalinized fibrous ground tissue pattern with numerous plasma cells was found, reminiscent of the organizing pneumonia-type pattern of pulmonary IP.<sup>2</sup> A myxoid ground tissue was reported in only 1 case. None of the further histopathologic features, such as the presence of calcifications or of giant cells, was restricted to a single entity. The immunohistochemical data of 9 previously published and the 3 present cases are summarized in Table 2.

### Therapy and Outcome

None of the previously published patients died from the IP, whereas 3 died from surgical or postsurgical complications. Treatment consisted of biopsy ( $n = 16$ ), or complete ( $n = 28$ ), or partial ( $n = 11$ ) resection, in some cases combined with corticosteroid treatment ( $n = 11$ ) and/or radiation therapy ( $n = 13$ ). Follow-up was reported for 40 previously published cases, 11 of them suffered local intracranial recurrences; these were combined with distant intracerebral recurrences in 2 cases and/or extracerebral recurrences in 3 cases. The extracerebral recurrences affected mediastinal structures ( $n = 2$ ), lung ( $n = 1$ ), carotic arteries ( $n = 1$ ), and nasal sinus ( $n = 1$ ). One other patient showed an isolated extracerebral subglottic recurrence (Table 1). Kaplan-Meier analysis of these 40 previously published cases and of the present 3 patients suggests that approximately 40% of the patients will suffer recurrences within 2 years of primary surgery (Fig 6). Only data on the intracerebral distribution of the lesions, patient age, basic ground tissue components, the quantity of plasma cells, treatment, and gender were available from nearly all these 43 patients, so that only these variables were included in the Cox regression analysis. In the univariate model ( $B$ , regression coefficient; SE, standard error; RR, risk ra-

**TABLE 1.** Histopathologic Data of 57 Patients With IP-CNS and of the Present 3 Cases\*

	Previous cases					New cases				
	Group A (n = 7)	Group B (n = 34)	Group C (n = 4)	Group D (n = 7)	Group E (n = 5)	Case 1	Case 2	Case 3 1 <sup>st</sup> res.	Case 3 2 <sup>nd</sup> res.	Case 3 3 <sup>rd</sup> res.
Ground tissue										
Fibrous	4	24		5	4	+++	+	+++	+++	++
Hyaline		6		1	1					
Myxoid	1									
Plasma cell density										
High	7	20	3	2	2					
Medium		10	1	2	3					
Low		2		3		+	+	+	+	+
Russel bodies	3	19	2	4						
Germinal centers	2	7		2	1					
Granulocytes	3	9	2		2					
Calcifications										
Total		4		3		+				
Psammoma		2		2		+				
Giant cells										
Multinucleated	1	1		2						
Foreign body		2								
Touton		1						+	++	+++
Necrosis		4		1			+			
Perivascular inflammation	4	4	3			+	++	+	+	+
Xanthomatous cells		1		1				+++	+	
Foamy cells	1	3	1				+	++	+	+

Abbreviation: res., resection.

\*Detailed description of the groups discussed in text.

tio; CI, 5% to 95% confidence interval; *P*, significance level) incomplete resection ( $B = 1.807$ ;  $P = 0.019$ ) and female gender ( $B = 1.407$ ;  $P = 0.018$ ) were found to be associated with a higher risk of recurrence. In the multivariate model, this was confirmed for both incomplete resection ( $B = 1.958$ ;  $SE = 0.781$ ;  $RR = 7.087$ ;  $CI = 1.535$  to  $32.72$ ;  $P = 0.012$ ) and female gender ( $B = 1.598$ ;  $SE = 0.615$ ;  $RR = 4.945$ ;  $CI = 1.483$  to  $16.493$ ;  $P = 0.009$ ) (Fig 6). Seven patients with local ( $n = 6$ ) or extracerebral ( $n = 1$ ) recurrence were treated with radiation ( $n = 3$ ), steroids ( $n = 2$ ), meth-

otrexate ( $n = 1$ ), azathioprine ( $n = 1$ ), and/or repeated surgery ( $n = 2$ ). Among these, a clinical cure was reported in 1 patient with resurgery only.

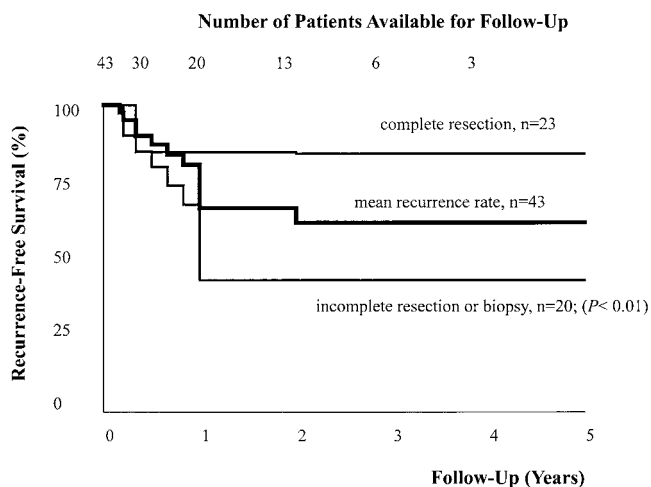
## DISCUSSION

IP-CNS represent a diagnostic and clinical challenge. Due to their nonspecific neuroradiologic and clinical findings,<sup>4</sup> the correct diagnosis depends on the postsurgical histopathologic examinations and on the

**TABLE 2.** Immunohistochemical Findings in Stromal Fibroblasts

	Vimentin	Smooth muscle actin	Desmin	Anaplastic lymphoma kinase
<b>IP-CNS</b>				
Figarella et al, 1990	n.d.	Positive	Negative	n.d.
Chang et al, 1991	Positive	n.d.	n.d.	n.d.
Sitton et al, 1992	Negative	n.d.	n.d.	n.d.
Chan et al, 1994	Positive	n.d.	n.d.	n.d.
Al Sarray et al, 1995	Positive	Positive	Negative	n.d.
Tresser et al, 1996	Positive	Positive	Positive	n.d.
Bramwit et al, 1997	Positive	focally positive	Negative	n.d.
Diederichs et al, 1998	n.d.	Positive	n.d.	n.d.
Hansen et al, 2001	Positive	Positive	Positive	n.d.
Present study case 1	Positive	Negative	Negative	Negative
Present study case 2	Positive	n.d.	n.d.	n.d.
Present study case 3	Positive	Positive	Negative	Positive
Total	9/10 (90%)	7/8 (88%)	2/7 (29%)	1/2 (50%)
<b>IP-nCNS</b>				
Coffin et al	112/114 (98%)	94/117 (80%)	63/117 (54%)	n.d.
Cook et al	n.d.	n.d.	n.d.	44/73 (60%)

Abbreviation: n.d., not done.



**FIGURE 6.** Increased recurrence rate after incomplete tumor resection as shown by Kaplan-Meier analysis ( $n = 43$ ; including the present 3 cases).

pathologist's awareness of this rare disease. The possibility of IP should be considered in all intracranial tumor-like lesions composed of a lymphoplasmacellular infiltrate and a collagenous stroma of varying density, regardless of additional features such as giant cells, calcifications, or the composition of the lymphocyte infiltrate. In contrast with IP-nCNS, where immunohistochemistry is of diagnostic impact (Table 2),<sup>3</sup> immunohistochemical data are available from only few patients with IP-CNS, so that its importance remains uncertain.<sup>4,13-19</sup>

With respect to differential diagnosis, classical CNS tumors, such as astrocytomas and primitive neuroectodermal tumors, are easy to identify, whereas further diseases may be more difficult to distinguish. Lymphoplasma cell-rich meningiomas, for instance, show fibrous ground tissue as well as mononuclear infiltrate, but the finding of meningeal whorls and positive EMA staining rules out IP-CNS. A lymphoma should be considered when the inflammatory component dominates, necessitating further analyses to rule out monoclonality. The intracranial extension of an orbital pseudotumor, which shows similar histopathologic features, should be ruled out by neuroimaging.<sup>11</sup> Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) may show an intracranial manifestation without nodal involvement.<sup>20</sup> As in patient 3, in whom it might have been inferred from the further histopathological findings, it should be precluded by the absence of S-100 antigen expression on histiocytes and of emperipolesis.<sup>20</sup> Finally, as seen from patient 3, who initially showed a typical IP-CNS, conversion to primary malignant fibrohistiocytic tumors can be ruled out only during follow-up studies.

This malignant transformation is also relevant to the hitherto unanswered questions of whether IP are primarily neoplastic lesions, whether malignant transformation occurs in distinct subentities, or whether patients with malignant transformation suffer from

completely different diseases, so that for this subgroup the term "inflammatory" might be misleading and should not be used any longer. Neoplastic transformation, (e.g., aggressive growth and additional distant lesions) have also been reported in IP-nCNS.<sup>1-3,6,21</sup> In patient 3, malignant transformation was observed after 5 years of follow-up, a time period that was available for only 3 of the 57 previously reported patients. Therefore, the risk of transformation may be higher than suggested by the literature. Also, an increasing number of studies are describing clonal cytogenetic changes in stromal fibroblasts,<sup>22,23</sup> suggesting a neoplastic nature in a considerable proportion of lesions. Some 60% of the inflammatory myofibroblastic tumors not affecting the CNS may express ALK, a characteristic that is well known from anaplastic large cell lymphomas, where it is explained by the t(2;5)(p23;q35) translocation at the ALK gene locus.<sup>24, 25</sup> From disease onset, ALK expression was also recorded in patient 3, whereas it was absent from pulmonary and CNS tissue of patient 1. Further studies on larger patient groups are needed to evaluate whether ALK expression characterizes a more aggressive subgroup of IP-CNS.

Apart from neoplastic transformation, the simultaneous occurrence of multiple lesions might also be caused by systemic (auto) immune mechanisms or infections with synchronous manifestations at predisposed sites. This postinfection hypothesis is supported by the isolation of viral DNA from IP-nCNS lesions (EBV, human herpesvirus 8)<sup>26,27</sup> and the presence of clinical or laboratory signs of systemic inflammation in 15% to 30% of the previous cases.<sup>3</sup> In IP-CNS the association with viral disease (EBV) has been reported only once,<sup>28</sup> and all of our PCR investigations proved negative. But these negative findings do not rule out a viral etiology; the viral load may have been too low, viruses not investigated might be involved, and viruses may have triggered inflammatory or even neoplastic processes before disappearing from brain tissue. Patient 2, for instance, showed a transient intrathecal synthesis of IgG antibodies to the herpes simplex virus, which was one reason for antiviral treatment. Because of the frequent association with hypergammaglobulinemia and autoimmune diseases,<sup>3,5,29</sup> autoimmune pathomechanisms have also been discussed in the literature, but could not be confirmed in the present cases either.

Vascular changes are common in IP-CNS. Circular fibrosis of small veins, for instance, was found in 6 previously published and in 2 of the present cases.<sup>13,19,30,31</sup> Whereas its etiology remains unknown, this fibrosis may reduce perfusion and enhance tissue destruction. Few patients with IP-nCNS showed invasion of hepatic or pulmonary veins by IP tumor tissue, leading to local thromboembolism.<sup>6,32</sup> In our cases, pulmonary venous invasion by IP tissue was recorded in patient 1, and hematogeneous propagation from the lung to the brain may have led to the cerebral manifestation in this patient. Although growth of IP tissue within cerebral vessels has not been described in the literature, the histopathologic findings in patients 1 and 2 suggest migration of mononuclear cells through vessel walls,



and vascular spread might account for the intracranial spread observed in patient 2. The third pattern of vascular involvement is characterized by the accumulation of mononuclear cells within Virchow-Robin spaces. It was recorded in 10 previous case and in all 3 new cases with IP-CNS.<sup>4,13,33-38</sup> On the one hand, this may mirror a reactive process; macrophages reside in Virchow-Robin spaces and, after contact with foreign antigens, such as viral antigens derived from deeper brain structures, they might initiate an inflammatory cascade with attraction of further mononuclear cells.<sup>39</sup> On the other hand, mononuclear cells also might migrate along Virchow-Robin spaces from inflamed to noninflamed tissue, recruiting an increasing amount of brain tissue.

Among the clinical and histopathologic characteristics, incomplete surgical resection and, astonishingly, female gender were found to be related to poorer outcome (Fig 6). However, the analyzed data were not collected prospectively, so that the presence of further prognostic factors cannot be ruled out, and even the relationship to different surgical approaches and to gender remains to be confirmed in larger prospective investigations. However, the high overall risk of recurrence and the deleterious consequences of progressive brain destruction merit frequent postsurgical brain imaging and most likely a radical surgical approach in the event of recurrence. Although suggested by single case reports, neither immunosuppression nor radiation therapy has hitherto been convincingly shown to be of prognostic benefit.

IP-CNS comprise a poorly characterized and rare group of combined fibrosing and inflammatory lesions of unknown etiology and with unsatisfactory treatment strategies. Collaborative prospective studies are needed to improve their histopathologic classification, to clarify their etiology, and to develop more effective treatment modalities.

## REFERENCES

- Coffin CM, Watterson J, Priest JR, et al: Extrapulmonary inflammatory myofibroblastic tumor: A clinicopathologic and immunohistochemical study of 84 cases. *Am J Surg Pathol* 19:859-872, 1995
- Matsubara O, Tan-Liu NS, Kenney RM, et al: Inflammatory pseudotumors of the lung: Progression from organizing pneumonia to fibrous histiocytoma or to plasma cell granuloma in 32 cases. *HUM PATHOL* 19:807-814, 1988
- Coffin CM, Humphrey PA, Dehner LP: Extrapulmonary inflammatory myofibroblastic tumor: A clinical and pathological survey. *Semin Diagn Pathol* 15:85-101, 1998
- Tresser N, Rolf C, Cohen M: Plasma cell granulomas of the brain: Pediatric case presentation and review of the literature. *Childs Nerv Syst* 12:52-57, 1996
- Biselli R, Boldrini R, Ferlini C, et al: Myofibroblastic tumours: Neoplasias with divergent behaviour. Ultrastructural and flow cytometric analysis. *Pathol Res Pract* 195:619-632, 1999
- Warter A, Satge D, Roeslin N: Angioinvasive plasma cell granulomas of the lung. *Cancer* 59:435-443, 1987
- Spencer H: The pulmonary plasma cell/histiocytoma complex. *Histopathology* 8:903-916, 1984
- Diss TC, Watts M, Pan LX, et al: The polymerase chain reaction in the demonstration of monoclonality in T cell lymphomas. *J Clin Pathol* 48:1045-1050, 1995
- Bai X, Hosler G, Rogers BB, et al: Quantitative polymerase chain reaction for human herpesvirus diagnosis and measurement of Epstein-Barr virus burden in posttransplant lymphoproliferative disorder. *Clin Chem* 43:1843-1849, 1997
- Felgenhauer K, Reiber H: The diagnostic significance of antibody specificity indices in multiple sclerosis and herpes virus-induced diseases of the nervous system. *Clin Investg* 70:28-37, 1992
- Garner A: Pathology of pseudotumours of the orbit: A review. *J Clin Pathol* 26:639-648, 1973
- Hosmer DWJ, Lemeshow S, Barnett V, et al (eds): Applied survival analysis: Regression modeling of time to event data. New York: Wiley, 1999
- Figarella-Branger D, Gambarelli D, Perez-Castillo M, et al: Primary intracerebral plasma cell granuloma: A light, immunocytochemical, and ultrastructural study of one case. *Neurosurgery* 27:142-147, 1990
- Chan YF, White J, Brash H: Metachronous pulmonary and cerebral inflammatory pseudotumor in a child. *Pediatr Pathol* 14:805-815, 1994
- Diederichs L, Kostovic N, Harzheim A, et al: Intracranial plasma-cell granuloma. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahren* 168:205-207, 1998
- Sitton JE, Harkin JC, Gerber MA: Intracranial inflammatory pseudotumor. *Clin Neuropathol* 11:36-40, 1992
- al-Sarraj S, Wasserberg J, Bartlett R, et al: Inflammatory pseudotumor of the central nervous system: Clinicopathological study of one case and review of the literature. *Br J Neurosurg* 9:57-66, 1995
- Bramwit M, Kalina P, Rustia-Villa M: Inflammatory pseudotumor of the choroid plexus. *Am J Neuroradiol* 18:1307-1309, 1997
- Chang Y, Horoupian DS, Lane B, et al: Inflammatory pseudotumor of the choroid plexus in Sjogren's disease. *Neurosurgery* 29:287-290, 1991
- Andriko JW, Morrison A, Colegial CH, et al: Rosai-Dorfman disease isolated to the central nervous system: a report of 11 cases. *Mod Pathol* 14:172-178, 2001
- Maier HC, Sommers SC: Recurrent and metastatic pulmonary fibrous histiocytoma/plasma cell granuloma in a child. *Cancer* 60:1073-1076, 1987
- Snyder CS, Dell Aquila M, Haghighi P, et al: Clonal changes in inflammatory pseudotumor of the lung. *Cancer* 76:1545-1549, 1995
- Su LD, Atayde-Perez A, Sheldon S, et al: Inflammatory myofibroblastic tumor: Cytogenetic evidence supporting clonal origin. *Mod Pathol* 11:364-368, 1998
- Cook JR, Dehner LP, Collins MH, et al: Anaplastic lymphoma kinase (ALK) expression in the inflammatory myofibroblastic tumor. *Am J Surg Pathol* 25:1364-1371, 2001
- Pulford K, Lamant L, Morris SW, et al: Detection of anaplastic lymphoma kinase (ALK) and nucleolar protein nucleophosmin (MPM)-ALK proteins in normal and neoplastic cells with the monoclonal antibody ALK1. *Blood* 89:1394-1404, 1997
- Arber DA, Kamel OW, van de Rijn M, et al: Frequent presence of the Epstein-Barr virus in inflammatory pseudotumor. *HUM PATHOL* 26:1093-1098, 1995
- Gomez-Roman JJ, Ocejio-Vinyals G, Sanchez-Velasco P, et al: Presence of human herpesvirus-8 DNA sequences and overexpression of human IL-6 and cyclin D1 in inflammatory myofibroblastic tumor (inflammatory pseudotumor). *Lab Invest* 80:1121-1126, 2000
- Fukunaga A, Yoshida K, Otani M, et al: Plasma cell granuloma extending from the extracranial to the intracranial space associated with Epstein-Barr virus infection. *Neurol Med Chir (Tokyo)* 38:292-296, 1998
- Coffin CM, Dehner LP: Fibroblastic-myofibroblastic tumors in children and adolescents: A clinicopathologic study of 108 examples in 103 patients. *Pediatr Pathol* 11:569-588, 1991
- Gartman JJ, Jr., Powers SK, Fortune M: Pseudotumor of the sellar and parasellar areas. *Neurosurgery* 24:896-901, 1989
- Le Marc'hadour F, Franssen P, Labat-Moleur F, et al: Intracranial plasma cell granuloma: A report of four cases. *Surg Neurol* 42:481-488, 1994
- Broughan TA, Fischer WL, Tuthill RJ: Vascular invasion by hepatic inflammatory pseudotumor: A clinicopathologic study. *Cancer* 71:2934-2940, 1993

33. Makino K, Murakami M, Kitano I, et al: Primary intracranial plasma-cell granuloma: A case report and review of the literature. *Surg Neurol* 43:374-378, 1995
34. Eimoto T, Yanaka M, Kurosawa M, et al: Plasma cell granuloma (inflammatory pseudotumor) of the spinal cord meninges: Report of a case. *Cancer* 41:1929-1936, 1978
35. Wilner HI, Vinas FC, Duffy C, et al: Magnetic resonance imaging of intracranial plasmocytic granuloma. *Skull Base Surg* 9:265-270, 1999
36. Kudesia S, Shankar SK, Das S, et al: Intracranial plasma cell granuloma: A report of four cases. *Neuro India* 46:142-146, 1998
37. Ferrer I, Garcia Bach M, Aparicio MA, et al: Plasma cell granuloma of the hypothalamic region. *Acta Neurochir (Wien)* 99: 152-156, 1989
38. Breidahl WH, Robbins PD, Ives FJ, et al: Intracranial plasma cell granuloma. *Neuroradiology* 38 (Suppl 1):S86-S89, 1996
39. Esiri MM, Gay D: Immunological and neuropathological significance of the Virchow-Robin spaces. *J Neurol Sci* 100:3-8, 1990