Plasma Cell Granuloma—An Enigmatic Lesion

Description of an Extensive Intracranial Case and Review of the Literature

Anna Maria Buccoliero, MD; Adele Caldarella, MD; Marco Santucci, MD; Franco Ammannati, MD; Pasquale Mennonna, MD; Antonio Taddei, MD; Gian Luigi Taddei, MD

• We present an unusual case of intracranial plasma cell granuloma in a 70-year-old man with a 6-month history of progressive visual disturbance. The lesion extensively involved the cranial base, extended into the frontal region, and reached the floor of the third ventricle in the suprasellar area. Microscopic examination of multiple diagnostic transsphenoidal biopsies showed an inflammatory proliferation with a predominance of cells that were immunohistochemically determined to be polyclonal plasma cells. Ultrastructural analysis confirmed the presence of numerous mature plasma cells in a mixed inflammatory proliferation. In situ hybridization for Epstein-Barr viral RNA revealed no evidence of viral expression. The patient was treated with steroid therapy and radiotherapy, without any appreciable reduction of the lesion's size. He is alive with persistent severe visual disturbance 14 months after the diagnosis. We discuss the etiopathogenetic, diagnostic, and therapeutic issues related to this entity, and review the literature.

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Plasma cell granuloma is a rare nonneoplastic lesion that was first described in 1973 by Bahadori and Liebow.[1] Histologically, this lesion is characterized by a cellular proliferation composed predominantly of polyclonal plasma cells, with a variable number of lymphocytes, neutrophils, eosinophils, and histiocytes, in a fibrovascular background.

Plasma cell granuloma occurs most often in the lung and conducting airways, but has also been found in other organs such as the spleen, stomach, pancreas, liver, thyroid, larynx, orbit, heart, kidney, and retroperitoneum. Intracranial and spinal cord plasma cell granulomas have also been described infrequently (a total of 38 cases). In exceptional cases, plasma cell granulomas have involved different organs in the same patient.[2–7]

This lesion's etiology, biologic behavior, and most appropriate treatments are unclear, and conflicting data have been reported.

We report an additional case of intracranial plasma cell granuloma that extensively affected the cranial base and the intracranial space.

REPORT OF A CASE

The patient, a 70-year-old-man with a 6-month history of progressive visual disturbance, was admitted to the Neurosurgical Service (Careggi Hospital, Florence, Italy) after a cerebral computed tomography scan and magnetic resonance imaging scan revealed a large intracranial lesion (Figure 1). The mass extensively involved the cranial base from the occipital condyles to the paranasal sinuses. The lesion extended for about 2 cm in the frontal region and reached the floor of the third ventricle in the suprasellar area; the optic nerves and the carotid arteries were completely covered by the lesion, but there was no vascular stenosis. Osteal erosion and hyperostosis were particularly evident in the maxillary sinuses. The mass showed homogeneous and dense contrast enhancement after contrast medium was administered. The preoperative differential diagnosis was pituitary tumor, chordoma, and plasmacytoma.

Laboratory examination of the patient's blood and urine did not reveal any hypergammaglobulinemia or Bence Jones proteinuria. Endocrinologic studies did not reveal any relevant abnormality in the secretion of pituitary hormones.

Regarding the patient's past medical history, he reported that he had experienced maxillary and frontal sinusitis for 3 years before admission to the hospital. Unfortunately, medical documentation of this symptom was not available.

Several transsphenoidal diagnostic biopsies were performed and showed a cellular proliferation composed predominantly of plasma cells.

The patient was treated with steroid therapy (dexamethasone by intramuscular administration; 8 mg twice a day for 1 week with progressive reduction of the dosage) and radiation therapy (30 Gy, 10 fractions in 2 weeks).

Successive radiologic scans did not reveal any remission or growth of the lesion.

The patient is alive with persistence of severe visual disturbance 14 months after the diagnosis.

MATERIALS AND METHODS

Tissue specimens were fixed in 10% buffered neutral formalin and embedded in paraffin. Osseous fragments were decalcified by exposure to 15% diluted hydrochloric acid overnight. Some 5-μm sections of each sample were stained with hematoxylin-eosin and periodic acid–Schiff (PAS) for morphologic evaluation; additional 5-μm sections were mounted on electrostatic slides and used for immunohistochemical studies (by the standard avidin-biotin peroxidase method). We used the following primary antibodies: monoclonal antibodies directed against CD45, CD20,

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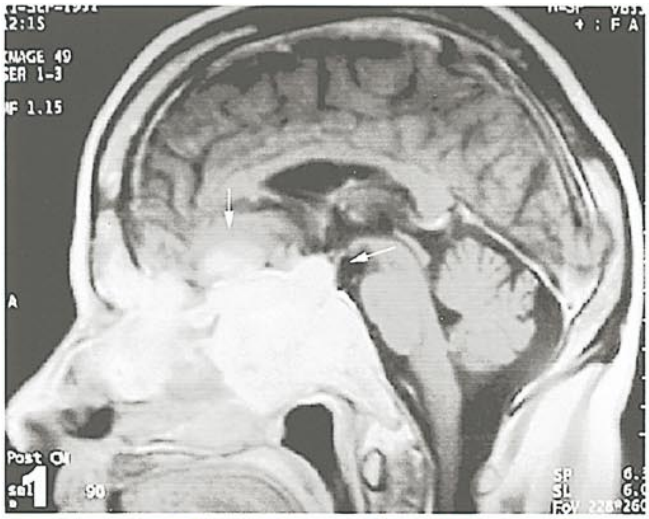
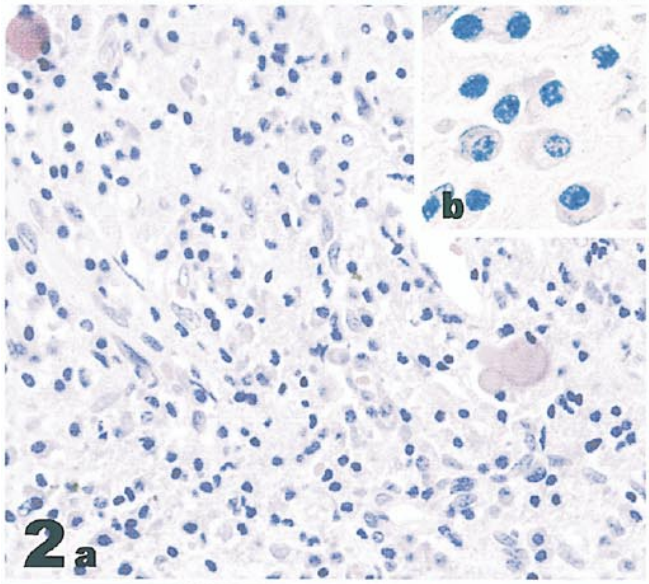
From the Dipartimento di Patologia Umana e Oncologia, Università degli Studi di Firenze, Firenze, Italy (Drs Buccoliero, Caldarella, Santucci, and G. L. Taddei); the Unità operativa di Neurochirurgia, Policlinico di Careggi, Firenze, Italy (Drs Ammannati and Mennonna); and the Dipartimento di Area Critica Medico-Chirurgica Sezione Chirurgia Generale e D.C., Firenze, Italy (Dr A. Taddei).

Corresponding author: Gian Luigi Taddei, MD, Dipartimento di Patologia Umana e Oncologia, Università degli Studi di Firenze, viale G.B. Morgagni, 85, 50134 Firenze, Italy (e-mail: gl.taddei@unifi.it).





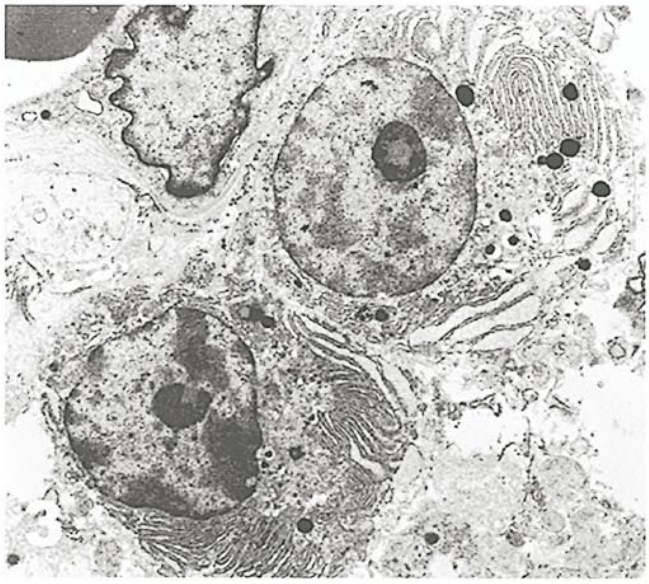


Figure 1. *A magnetic resonance imaging scan with contrast enhancement revealed a lesion (arrows) extensively involving the cranial base, extending in the frontal region, and reaching the floor of the third ventricle.*

Figure 2. *An inflammatory infiltrate composed mainly of mature plasma cells (a, b). Russell bodies were present (a) (hematoxylin-eosin, original magnifications ×200 [a] and ×1000 [b]).*

Figure 3. *An ultrastructural study of the plasma cells showed the characteristic eccentric nucleus with clumped nuclear chromatin and well-developed rough endoplasmic reticulum (uranyl acetate and lead citrate, original magnification ×8000).*

CD68, Ki-67, κ and λ light chains, and epithelial membrane antigen (EMA), and polyclonal antibody directed against CD3. Antibody sources, clones, and dilutions, and methods of antigen retrieval are shown in the Table. Immunohistochemical staining was performed on a NEXES automated immunostainer (Ventana Medical Systems, Tucson, Ariz) (CD45, CD3, CD20, CD68, Ki-67, EMA) and on a GENOMIX automated immunostainer (BioGenex, San Ramon, Calif) (κ and λ light chains).

An additional 10-μm section of each sample was used for an Epstein-Barr RNA in situ hybridization study (EBER probe; BioGenex). After enzymatic predigestion (proteinase K, 37°C, 15 minutes) and peroxidase inhibition (H_2O_2, 3%, 10 minutes), one drop of the probe was applied to the tissue section (55°C, overnight); then, an antibody against fluorescein (BioGenex; room temperature, 20 minutes) was applied. Finally, the GenPoint system (Dako, Glostrup, Denmark) was used as a catalyzed amplification system.

Tissue for electron microscopy was obtained from the paraffin block, postfixed in osmium tetroxide, dehydrated in graded ethanol, embedded in epoxy resin, and cut with a diamond knife in a Leica Ultracut R microtome (Leica Microsystems, Wien, Austria). Ultrathin sections were stained with uranyl acetate and lead citrate, and viewed with a Philips 410 LS transmission electron microscope (Philips' Gloeilampenfabrieken, Eindhoven, Netherlands).

RESULTS

Histopathologic examination of the lesion revealed an inflammatory infiltrate composed mainly of mature plasma cells and PAS-positive Russell bodies interspersed in a loose fibrous tissue (Figure 2). There were no epithelioid granulomas or giant cells. Areas of necrosis and hemorrhage, and mitotic figures were absent.

On immunohistochemistry, the plasma cells were immunoreactive for EMA and for both κ and λ light chains, whereas antibodies against CD45, CD3, CD20, and CD68 reacted with scattered B and T lymphocytes and macrophages.

In situ hybridization for Epstein-Barr viral RNA did not reveal any evidence of viral expression.

Ultrastructural examination, performed on tissue from paraffin blocks, notwithstanding the diffuse regressive change, showed abundant inflammatory cellularity with a predominance of mature plasma cells. They characteristically had an eccentric nucleus with clumped nuclear chromatin, well-developed rough endoplasmic reticulum (which occasionally contained the Russell bodies, appearing as round, electron-dense bodies), and a prominent Golgi apparatus (Figure 3).

The cells constituting the lesion had no clearly demonstrable desmosomes, complex interdigitations of the plasma membrane, or cytoplasmic filaments.

COMMENT

Plasma cell granuloma is an unusual nonneoplastic lesion. It consists of a proliferation of inflammatory cells, with a predominance of plasma cells, in a fibrovascular background. Its exact incidence is unclear because of the

Sources, Clones, and Dilutions of Antibodies, and Methods of Antigen Retrieval*				
Antibody	**Source**	**Clone**	**Dilution**	**Method of Antigen Retrieval†**
λ Light chains	BioGenex (San Ramon, Calif)	HP6054	1:300	Protease 0.05% (10 min)
κ Light chains	BioGenex	L1C1	1:2000	. . .
CD45	Dako (Glostrup, Denmark)	2B11; PD7/26	1:400	Microwave 300 W (in TEC, 35 min)
CD3	Dako	Polyclonal	1:50	Microwave 300 W (in TEC, 35 min)
CD20	Dako	L26	1:400	Microwave 300 W (in TEC, 35 min)
CD68	Dako	PGM1	1:50	Microwave 300 W (in TEC, 35 min)
EMA	Dako	E29	1:50	Citrate buffer 10mM, pH 6.0 (30 min)
Ki-67	IMMUNOTECH (Marseille, France)	MIB-1	1:80	Microwave 300 W (35 min)

* EMA indicates epithelial membrane antigen; TEC, Tris EDTA–citrate buffer, pH 7.8.

† For methods that involved microwaving, microwaving was performed with the MICROMED T/T MEGA-MILESTONE Srl (SORISOLE, Bergamo, Italy).

numerous different terms by which it is called (ie, inflammatory myofibroblastic tumor, inflammatory pseudotumor, inflammatory myofibroblastic tumor, inflammatory myofibrohistiocytic proliferation, xanthomatous pseudotumor).

Occurrence of this lesion in intracranial and spinal sites is particularly infrequent. Thirty-eight prior cases in these sites have been reported (70% male patients, 30% female patients; median age, 32 years; range, 5–76 years). Seventy-three percent of these cases occurred in people younger than 41 years. In the majority of the patients, a single intracranial plasma cell granuloma (31 cases, 82%) or spinal plasma cell granuloma (1 case, 3%)[8] was detected, whereas infrequently (6 cases, 16%), multiple synchronous or metachronous lesions were documented.[2–7] Four of these last 6 patients had both pulmonary and intracranial lesions,[3–6] and 2 had both intracranial and spinal cord lesions.[2,7]

The locations of the previously reported primary intracranial plasma cell granulomas have varied (ie, meninges, cerebral hemispheres, ventricles, hypothalamus, sellar region, cerebellum). A secondary intracranial extension of an extracranial plasma cell granuloma has also been described.[9]

These data indicate that intracranial and spinal plasma cell granuloma is typically a variably located primary solitary lesion that predominantly affects young men.

In contrast, there are only limited data available on the etiology, pathogenesis, and most effective treatment. Consequently, little is known about the prognosis.

Some authors consider plasma cell granuloma to be a purely inflammatory lesion related to infection or an autoimmune disorder.[3,9–11] Although cases associated with bacterial or fungal infection have been reported, some in situ hybridization studies have revealed the presence of the Epstein-Barr virus in a large number of inflammatory pseudotumors, suggesting a possible important role of this virus in the etiopathogenesis of these tumors.[9–11]

The most common treatment for plasma cell granuloma is a complete resection; however, in some cases, total surgical excision is not possible. Radiotherapy and/or steroid therapy have sometimes been successfully used to treat patients with nonresectable lesions, but discordant results have also been reported.

With respect to prognosis, plasma cell granuloma seems to be a generally benign, nonrecurring condition; nevertheless, local aggressiveness and recurrences may complicate the outcome of the disease.

An additional problem is related to the possible difficulties of differential diagnosis. A common preoperative diagnosis for this lesion is meningioma, but a preoperative diagnosis of plasmacytoma, chordoma, craniopharyngioma, or pituitary adenoma is occasionally made, depending on the location of the lesion.[12–15] From a histopathologic point of view, plasmacytoma and meningioma, particularly in its ''lymphoplasmacyte-rich'' variant, should be excluded first. In addition to an accurate histologic study, immunohistochemical and eventually ultrastructural studies can help in the differential diagnosis. The immunohistochemical polyclonality of the plasma cells excludes the diagnosis of plasmacytoma. Differentiating a plasma cell granuloma from a lymphoplasmacyte-rich meningioma can be difficult on the basis of light microscopy and immunohistochemical findings alone: the histiocytes in the plasma cell granuloma may mimic meningothelial cells, and plasma cells are polyclonal in both of these lesions. Consequently, the absence of the ultrastructural features of meningioma (ie, well-developed desmosomes and pronounced cytoplasmic interdigitations) should be ascertained.[8,12]

Our present case of plasma cell granuloma is noteworthy for the age of occurrence, the wide extension, the absence of demonstrable Epstein-Barr virus infection, and the lack of responsiveness to steroid therapy and radiotherapy.

We believe that because of the rarity of plasma cell granuloma, especially in the intracranial location, each new case should be recorded to allow a better understanding of this enigmatic lesion.

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