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Clear cell meningioma with PEC-oma characteristics. Immunohistochemical and ultrastructural study of a case

Meningioma a cellule chiare con i caratteri del PEC-oma. Studio immunoistochimico ed ultrastrutturale di un caso

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Summary

***Aim*. The Authors deem it opportune to report a case of clear cell meningioma with the morphological, immunohistochemical and ultrastructural features of a perivascular epithelioid cell tumour (PEC-oma). The interest in this finding is due not only to the low frequency of clear cell meningiomas, but above all to the fact that it presents nodular aspects with a concentric arrangement of the cells around a vessel and with positivity for smooth muscle actin and for the melanogenic antigen HMB-45. *Materials and methods*. Multiple fragments of this tumour underwent histological, immunohistochemical and electron microscopy investigation. *Results*. The morphological results showed nodules with a presence in peri-vascular location of medium-sized ovoid elements with a large clear cytoplasm and, along the periphery, of spindle-shaped elements with a dense cytoplasm. These histopathological findings were confirmed ultrastructurally; this technique showed, in the cytoplasmic matrix, intermediate filaments, varying amounts of organules, junctions, and real and**

Riassunto

***Finalità*. Gli Autori hanno ritenuto opportuno riportare un caso di meningioma a cellule chiare avente i caratteri morfologici, immunoistochimici ed ultrastrutturali del PEC-oma (*perivascular epithelioid cell tumour*). L'interesse di questo reperto è rappresentato non solo dalla scarsa frequenza dei meningiomi a cellule chiare, ma soprattutto dal fatto che esso presenta aspetti nodulari con una disposizione concentrica delle cellule attorno un vaso e con una positività per l'actina-muscolo liscio e per l'antigene melanogenetico HMB-45. *Materiali e metodi*. Frammenti molteplici di tale neoplasia sono stati sottoposti a tecniche di istologia, immunoistochimica e di microscopia elettronica. *Risultati*. I risultati morfologici hanno messo in evidenza noduli con presenza in sede peri-vascolare di elementi ovoidali di media taglia con citoplasma ampio e chiaro e lungo le fasce periferiche di elementi fusati con citoplasma compatto. Questi reperti istopatologici sono stati confermati all'esame ultrastrutturale; mediante questa tecnica è stato possibile evidenziare nella matrice citoplasmatica filamenti intermedi, quote**

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virtual intercellular spaces. The immunohistochemical investigation showed high positivity for vimentin, positivity in 60% of the cells for the HMB-45 antigen, and positivity in 40% of the cell population for the smooth muscle actin. *Conclusions*. The application of complementary morphological techniques showed features that go beyond those of clear cell meningioma and are indicative of a PEC-oma. In applying this diagnosis the Authors appreciate the necessity for caution in the presentation of this finding because it is a single case with objective diagnostic difficulty and because of the numerous current interrogatives surrounding PEC-omas. Eur. J. Oncol., 13 (2), 103-113, 2008

Key words: **meningioma, clear cytoplasm, intermediate filaments, junctions, intercellular spaces**

variabili di organuli, strutture giunzionali, e spazi intercellulari reali e virtuali. Le indagini di immunoistochimica hanno documentato l'esistenza di un'intensa positività per la vimentina, positività per il 60% delle cellule per l'antigene HMB-45 e una positività del 40% della popolazione cellulare per l'actina muscolo-liscio. *Conclusioni*. L'applicazione di metodiche morfologiche tra loro complementari ha messo in evidenza, nel caso in esame, caratteri che travalicano quelli del meningioma a cellule chiare e sono suggestivi di un PEC-oma. Nel porre questa diagnosi gli Autori riconoscono la necessità di molta cautela nella presentazione di questo reperto sia per la sua unicità, sia per le oggettive difficoltà diagnostiche, sia per i numerosi interrogativi riguardanti i PEC-omi. Eur. J. Oncol., 13 (2), 103-113, 2008

Parole chiave: **meningioma, citoplasma chiaro, filamenti intermedi, giunzioni, spazi intercellulari**

Introduction

The classification of cerebral tumours by the World Health Organization (WHO) includes, among the meningiomas, also the clear cell form; this is characterised by the presence in varying quantities of cells with a clear transparent cytoplasm. This characteristic is due to the accumulation of glycogen both attached to the membranes and also free in the cytoplasmic matrix[1]. These deposits have been considered important toward the morphogenetical grouping of neoplasms with different topography and histogenesis.

Neoplasms with this phenotypical feature can be found in all organs, although with very different biological identity and behaviour. Clear cell meningiomas can also be part of this heterogeneous group.

This form of meningioma is considered rare, aggressive and difficult to diagnose and can show frequent recurrences and/or metastases[2,3].

A review of the literature shows the importance of this factor; Kakita *et al*[4] diagnosed a case of clear cell meningioma, underscoring the importance of the ultrastructural examination for a certain diagnosis of this histotype.

In the same year, Zorludemir *et al*[5] showed the histopathological features of this tumour, emphasizing the presence of sheets of PAS-positive cells. With reference to the particular aggressiveness of clear cell meningioma, Kubota *et al*[6] described a case of clear cell meningioma that recurred three times with the same characteristics.

As regards the topographical distribution, the preferential sites of this histotype are the posterior cranial fossa and the spine marrow, but cases in other sites have been described[7].

Harada *et al*[8] described a case in the literature of clear cell meningioma arising in the cells of the arachnoid surrounding a branch of the trigeminus. Alameda *et al*[9] found a case of clear cell meningioma with "chordoid" features.

Payano *et al*[10] documented two cases located in the *cauda equina*. Dhall *et al*[11] reported a case of a tumour with the above-mentioned characteristics in the *dura mater spinalis* with a soprasellar recurrence. As already stated, this characteristic of a "clear cytoplasm" is not only an element of distinction and identification, but also a cytological factor of belonging to the group of clear cell tumours due to glycogen accumulation. This group, which also

includes the clear cell meningioma, has recently been reclassified because of unexpected antigenic properties identified immunohistochemically.

This reinterpretation of the morphological findings, in the light of the immunohistochemical data, has led to the discovery of a new histotype: perivascular epithelioid cell tumours or myo-melanocyte clear cell tumours (PEC-omas).

This is a difficult to classify heterogeneous group of tumours, recently acknowledged by the WHO; it is characterised morphologically by cells arranged around the capillaries and post-capillary venules like pericytes, whereas immunohistochemically it shows, in these cells, positivity for smooth muscle actin and for the melanocytic antigen HMB-45[12]. The morphological profile is polymorphous for the presence of roundish, ovoid, spindle-shaped or simply polygonal elements; they are mesenchymal, ubiquitous and include very different clear cell stromal tumours such as angiolipomas, lympho-angioleiomyomas and clear cell melanocytic tumours[12-14].

This new group of tumours is not only morphologically and histogenetically heterogeneous, it is also ubiquitous and can involve all organs or tissues, as seen from the relative data in the literature; Ribalta *et al*[15] reported a case of clear cell tumour of the kidney that was positive for HBM-45, the S100 protein, actin and vimentin.

Hashimoto *et al*[16] described a nodular formation of the lung made up of clear cells in a perivasal arrangement; these elements showed clear positivity for HBM-45 and CD56.

Bonetti *et al*[17] described a case of malignant PEC-oma associated to tuberous sclerosis.

Pan *et al*[18] presented a case of this tumour in the bladder with epithelioid-like cells with a clear cytoplasm.

Genevay *et al*[19] reported a case of PEC-oma of the cecum and the pararectal area; the cell population of this formation had epithelioid features and positivity for HBM-45 and actin.

Pileri *et al*[20] described two cases of PEC-oma of the lung with cells full of glycogen, containing HBM-45 antigens and smooth muscle actin.

Cases of PEC-oma have been reported of the skin[21], duodenum[22], uterus[23], pelvic region[24], bladder[25], kidney[26], oral cavity[27], colon[28], pancreas[29], etc.

This brief, albeit incomplete, review of cases of PEC-omas is useful to underscore how in these tumours the qualifying and unifying rôle of the immunohistochemical data is primary compared to the morphological and histogenetic findings. In fact, by applying antigenic staining, it is possible to group different and distant neoplastic forms, on the basis of molecular properties that go beyond the established confines of the single cytotypes.

The authors of this article deem it opportune to describe a case of clear cell meningioma studied with histological, ultrastructural and immunohistochemical methods; the set of results are interesting and worthy of report, as they indicate the possible existence of a clear cell meningioma with features of a PEC-oma.

Case report

A 70-year-old man presented with intracranial hypertension, right hemiparesis and dysphasia. The patient underwent surgical procedure with pace-maker placement for sinus bradycardia; initial brain CT scan with contrast enhancement showed a 2 cm dural-based mass in the left frontal convexity (fig. 1 A, B). Meningioma was diagnosed, and gross total resection of the main mass was performed. A postoperative CT scan showed removal of the lesion (fig. 1 C, D).

Materials and methods

The sample from the case under examination was divided in order to study part of it with a light microscope and the other part with a transmission electron microscope. The fragments used for light microscopy were first fixed in 10% formalin (buffered at pH 7.2 with 0.2 M phosphate buffer) and subsequently embedded in paraffin. Sections were cut from the single blocks for the histological and immunohistochemical analysis. The following histological methods were used: haematoxylin-eosin (H-E) E-v Gieson, PAS, trichrome according to Mallory, silver stain according to Gömori for the reticulum.

The following antigens were determined with monoclonal antibodies: vimentin, fibronectin, Ki67, p53, CD34, VEGF, smooth muscle actin, CD56 and HMB-45.

The fragments used for transmission electron microscope were fixed in 4% paraformaldehyde, diluted with 0.2 M phosphate buffer, pH 7.4, and subsequently post-fixed in 1% osmium tetroxide, diluted in the same buffer and then embedded in Epon resin. One-micron-thick semifine sections were cut from these blocks and stained with toluidine blue; after evaluation of the samples, ultrafine sections

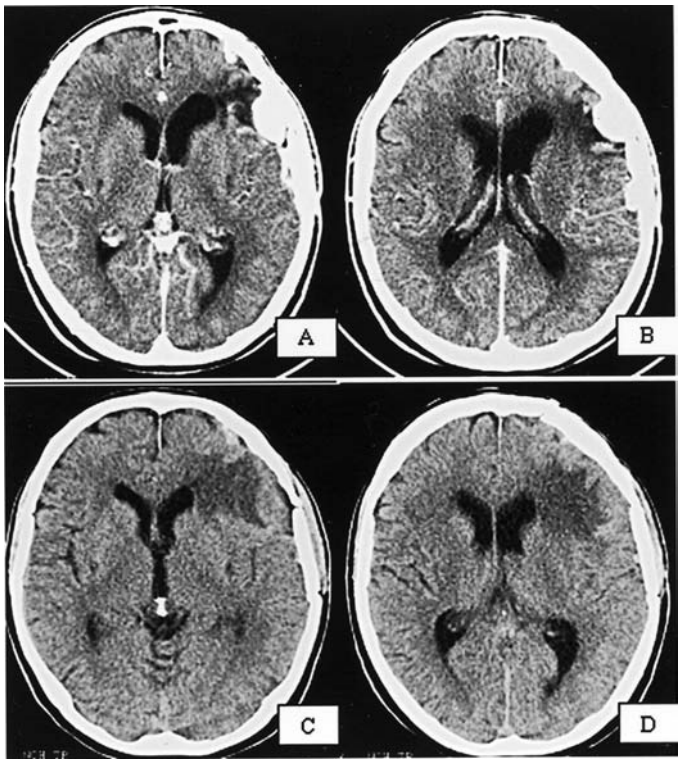

Fig. 1. CT scan with contrast enhancement showing preoperative aspects of meningiomas in A and B. Postoperative examination demonstrating a complete removal of the tumour in C and D

were cut from the same blocks and contrasted with uranyl acetate.

Results

Histopathology

The tumour under study had an architecture of confluent nodules of different sizes, each with a dense appearance, surrounded by fine fibrotic filaments and with a vessel of varying sizes in the centre (fig. 2).

The cell population had a medium-to-high density, was arranged in bands and was made up of two phenotypically distinct cytotypes, although there were elements with intermediate characteristics. The first type was located mainly along the periphery of the single nodules and was made up of groups of spindle-shaped, small to medium-sized cells with a small dense cytoplasm (fig. 3); the second cytotype, more numerous, was located in the central area, and was made up of medium-sized, ovoid elements with a large clear cytoplasm surrounded by a distinct cell membrane (fig. 3).

Amidst these two cytotypes, there were elements with different degrees of transition, due to gradual differences not only in the form and volume of the cells, but in particular in the process of diaphanization of the cytoplasm. PAS showed cytoplasmic positivity of the cells at the initial or intermediate stages of diaphanization, while the very clear, bloated, almost balloon-like cells showed poor PAS positivity, most likely due to a concomitant hydropic swelling with leakage of the contents to the outside (fig. 4).

The centre of each nodule was occupied by a vessel, generally a post-capillary venule, around which were gathered, in a sleeve-like fashion, cells with a clear cytoplasm, similar to pericytes (fig. 4). These elements touched and had a pleomorphous profile; the intercellular spaces were occupied by acidophilic, amorphous material. The nuclei were centred, slightly dysmorphic and had a prominent nucleole (fig. 5). No atipia and/or mitoses were found.

Ultrastructural findings

The two above-mentioned cytotypes could also be seen ultrastructurally, as could the elements with different degrees of intermediate characteristics (fig. 6).

The spindle-shaped elements had a dense cytoplasmic matrix, rich in intermediate filaments, mitochondria and ergastoplasmic structures; the cells with a large clear cytoplasm had scanty organules and thin bands of intermediate filaments (fig. 7). All the cells were linked by junctions and desmosomes, and often the intracellular spaces were occupied by deposits of amorphous, hyaline material (fig. 8).

Immunohistochemical findings

The antigen staining gave the following results:

– Vimentin
  The cells were vimentin-positive in various degrees; positivity was high in the cells with dense cytoplasm, low in the elements with clear cytoplasm, and of varying degrees in the cells with ongoing clarification (fig. 9).

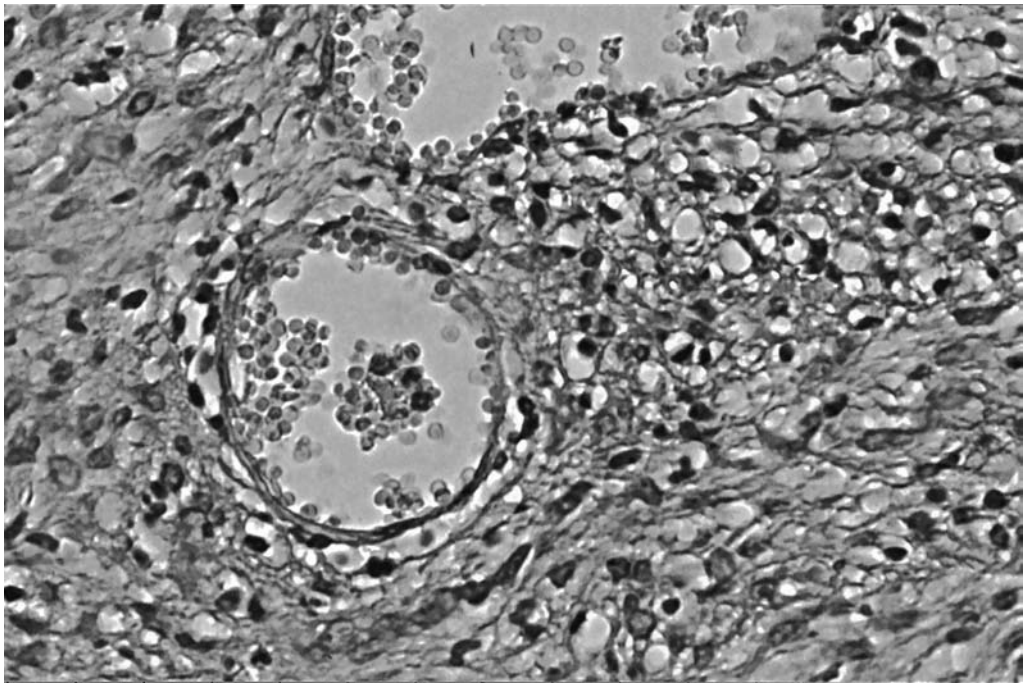

Fig. 2. Clear cell meningioma: histology
Pseudo-nodular formation with arrangement of the cells in concentric layers around a small vessel; the cytoplasm is frequently clear and the nuclei are hyperchromatic and pleomorphous
H-E, 200x

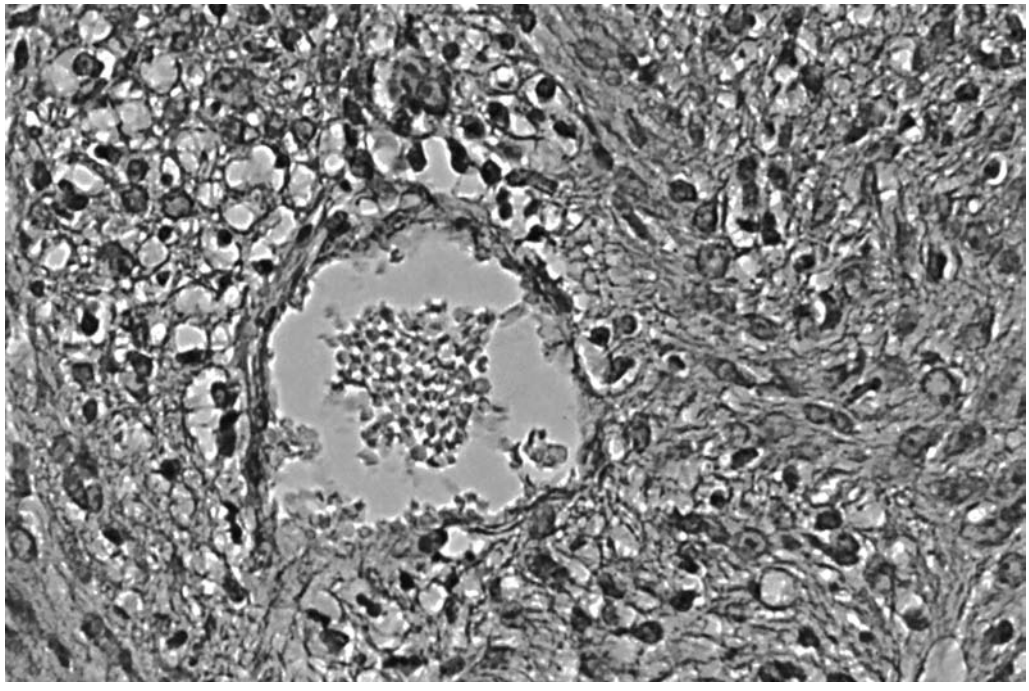

Fig. 3. Clear cell meningioma: histology
"Pericytic" arrangement around a blood vessel of cells with large diaphanous cytoplasm and pleomorphous nucleus. On the periphery, bands of spindle-shaped elements with a dense cytoplasm can be seen
H-E, 200x

– Ki67
  Positivity of this antigen was around 30% of the cell population; this could be seen by foci gathered mainly along the periphery of the nodules.
– p53
  Positivity of this antigen involved both the clear cells and those with a dense cytoplasm; positivity was found in 80% of the cell population.
– p27
  Nuclear positivity was found in 40% of the cell population with an even distribution of both of the above-described cytotypes.
– VEGF
  Clear widespread positivity of the cytoplasms of the endothelia that were bloated, enlarged and bulging in the lumen. The positivity levels were higher in the areas of neoangiogenesis.

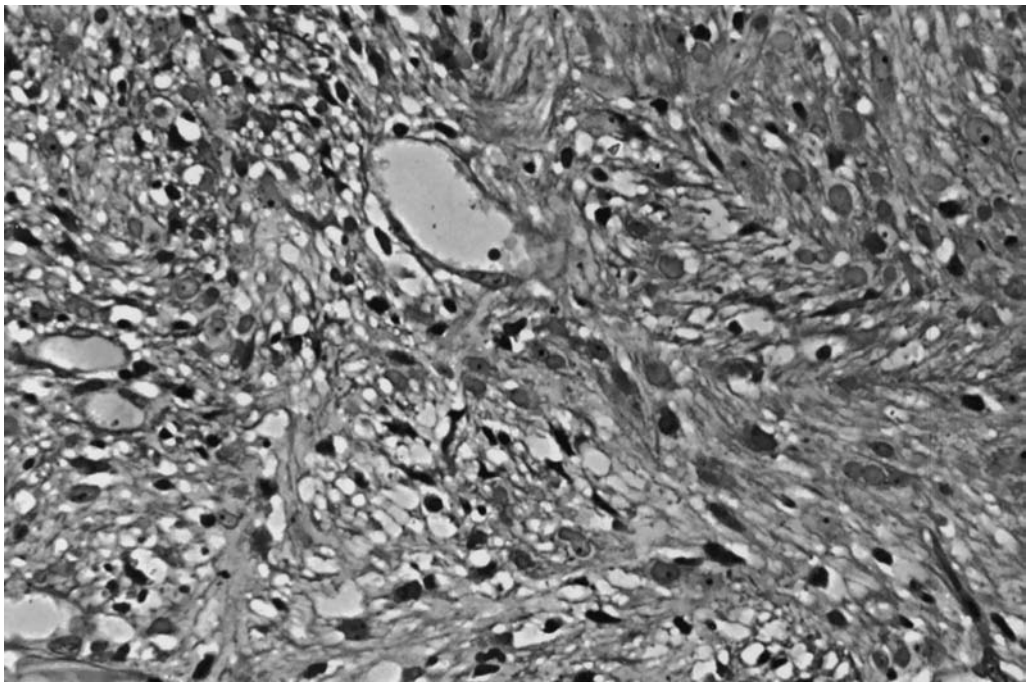

Fig. 4. Clear cell meningioma: histology
Pleomorphous cell population with clear cytoplasm around a small vessel: spindle-shaped, roundish, irregular elements with varying degrees of vacuolization and often with enlarged hyperchromatic nucleus
Toluidine blu, 200x

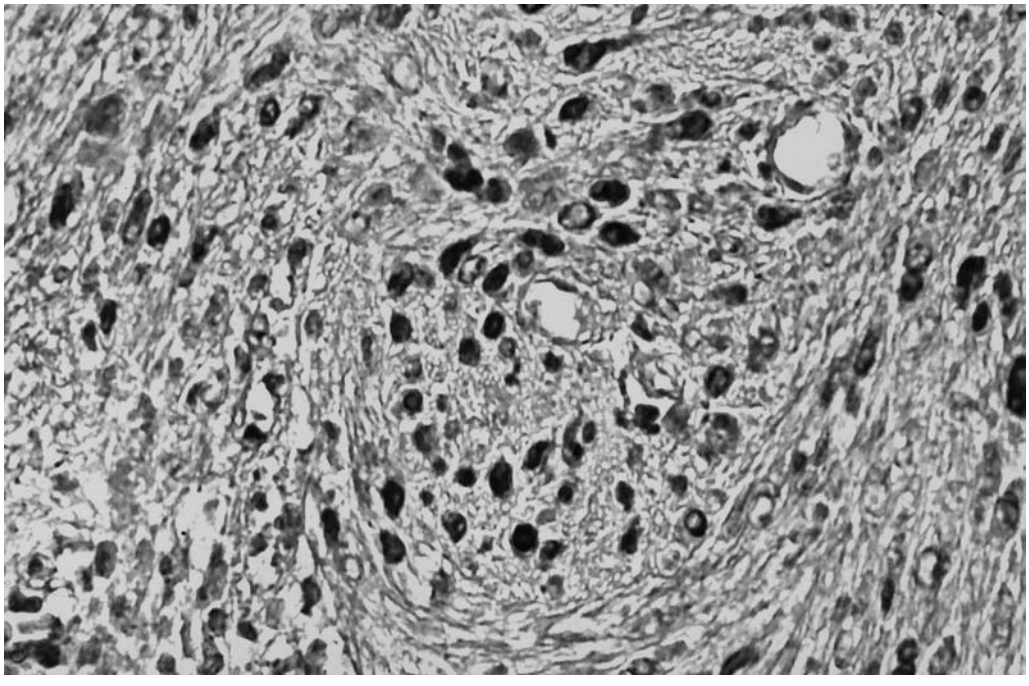

Fig. 5. Clear cell meningioma: histology
Meningeal cells with clear cytoplasm; dysmorphic nuclei and prominent nucleoles
Toluidine blu, 630x

– p21
Nuclear positivity of 30%, both in the clear cells and in the dense cells, mainly due to the nuclei that were bulky, hyperchromatic and dysmorphic.
– CD34
High positivity of the vessels with involvement of the endothelia, the basal membrane and the perivascular tissues. The single capillaries in development and those with virtual lumen were visible, with clear appearance of the hypervascularized micro-areas due to neoangiogenesis (fig. 10).
– HMB45
Positivity for this antigen in 60% of the cell population: mainly present in the clear cells, and slightly less in the cells with a dense cytoplasm.

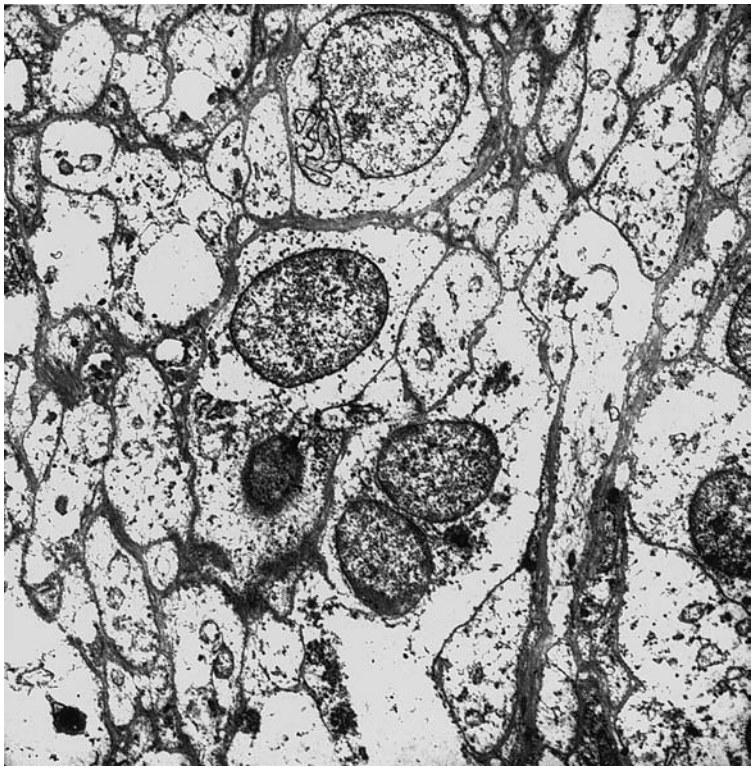

Fig. 6. Clear cell meningioma: electron microscopy
Aggregates of meningeal elements with globally transparent cytoplasm and scanty organules. Presence of bi-nucleated elements
Lead citrate-uranyl acetate, 4400x

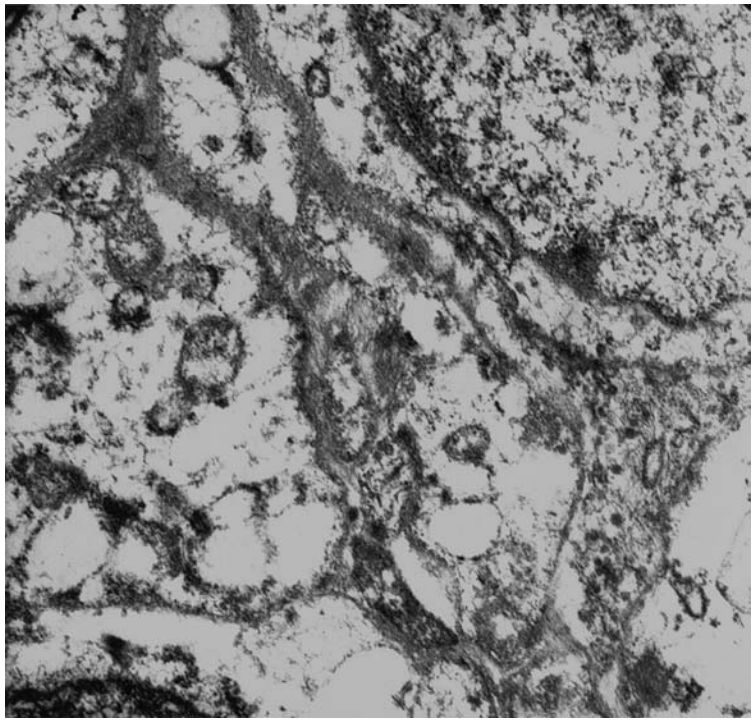

Fig. 7. Clear cell meningioma: electron microscopy
The cytoplasm is poor in or is devoid of organules, only intermediate filaments remain
Lead citrate-uranyl acetate, 8000x

– Actin
Clear positivity for actin in 40% of the cell population: seen more frequently in the elements with dense cytoplasm (fig. 11).
– Oestrogen
Positivity in 15% of the cell population: cytoplasmic positivity both of the cytoplasm of the dense cells and of the cytoplasm of the cells undergoing diaphanization.
– Progesterone
Positivity in 85% of the cases, often of the cytoplasm both of the dense cells and of those with a clear cytoplasm.

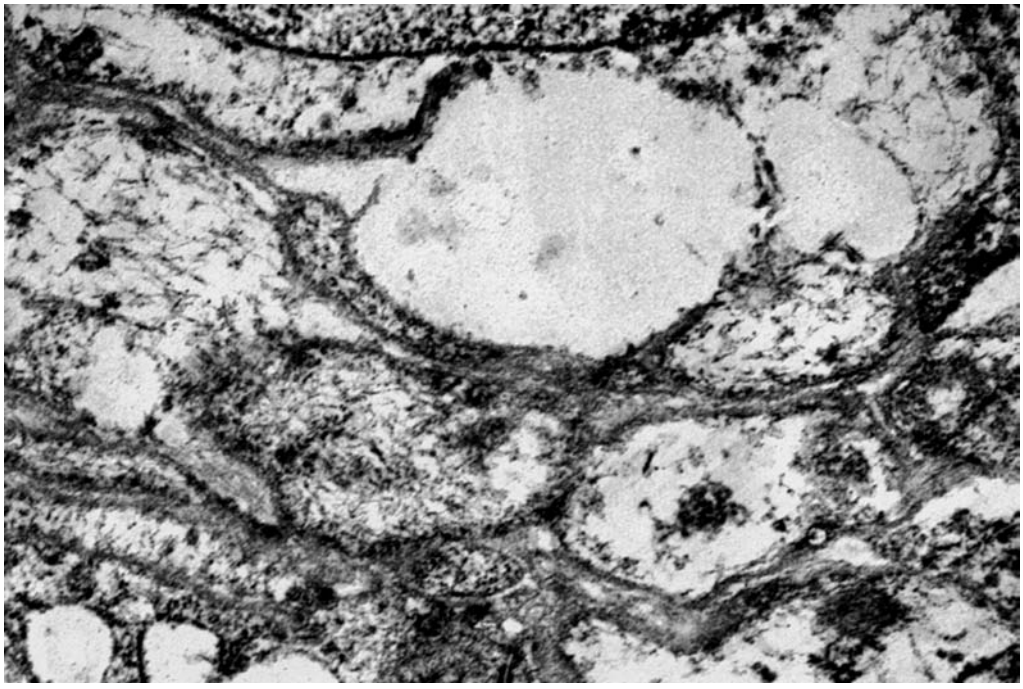

Fig. 8. Clear cell meningioma: electron microscopy
The meningeal elements have junction gaps and desmosomes. In some places the intercellular spaces are real and contain amorphous material mixed with fibrils
Lead citrate-uranyl acetate, 8000x

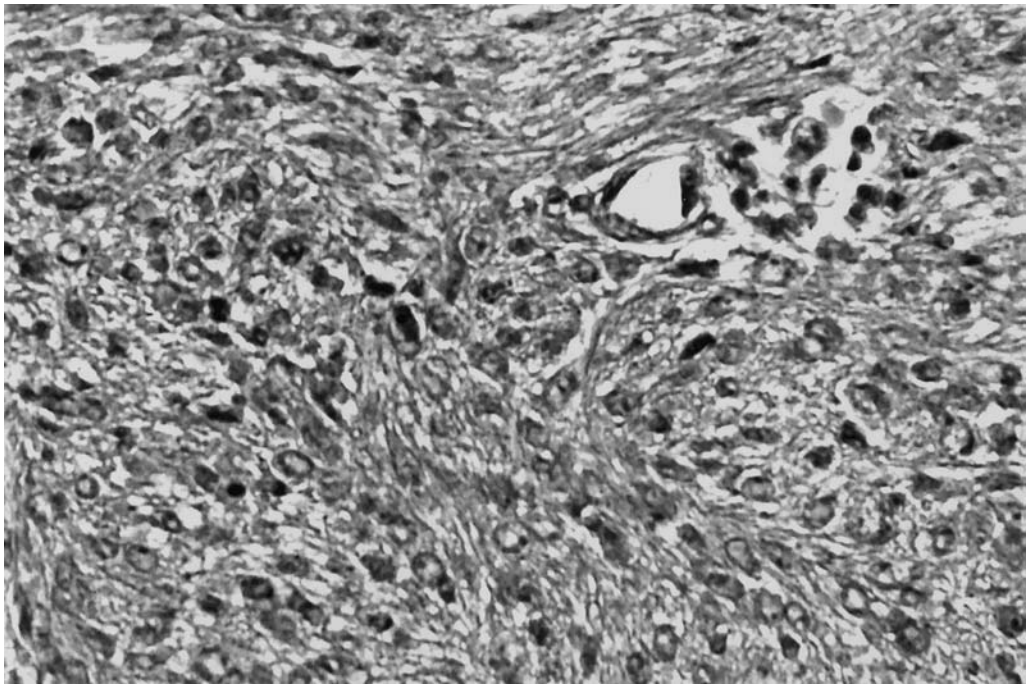

Fig. 9. Clear cell meningioma: immunohistochemistry
The vimentin stain shows this antigen almost exclusively in the elements with a dense cytoplasm
Vimentin, 630x

Comment

The application of complementary morphological methods such as histology, electron microscopy and immunohistochemistry has shown in the case under study features that go beyond those of clear cell meningioma and are indicative of PEC-oma.

On a morphological level, the cells have a perivascular arrangement, a clear cytoplasm, are PAS-positive and contain, besides vimentin-positive filaments, also filaments positive for smooth muscle actin and for the melanocytic protein HMB-45.

The authors of this article are aware of the caution necessary in presenting this finding because it comes from one single case, because of the obvious diagnostic difficulty and, of no lesser importance, because of the numerous questions concerning the definitive nosographical designation of PEC-omas.

As mentioned in the introduction, PEC-omas are tumours of a mesenchymal nature and are ubiqui-

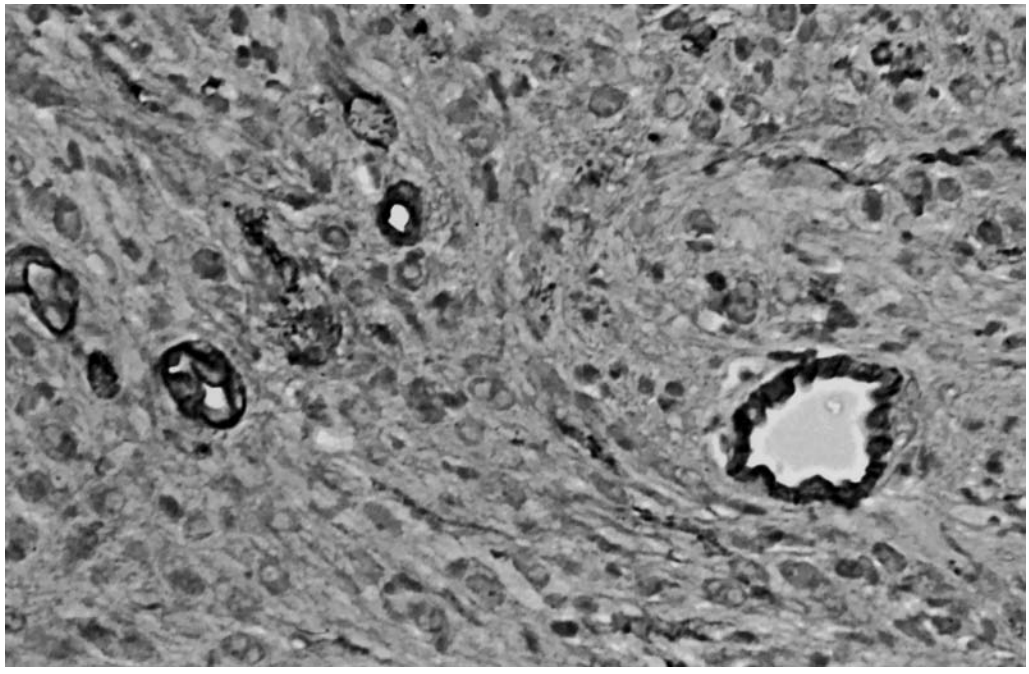

Fig. 10. Clear cell meningioma: immunohistochemistry
The CD34 antigen stain shows several small newly-formed vessels (neoangiogenesis)
CD34, 200x

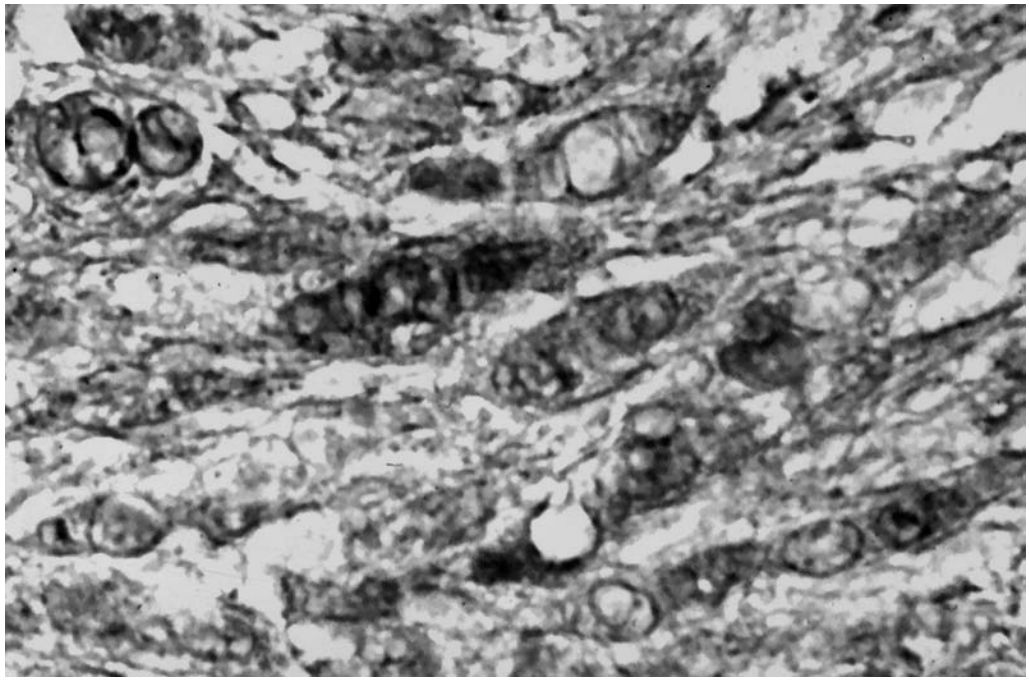

Fig. 11. Clear cell meningioma: immunohistochemistry
The smooth muscle actin antigen stain shows varying positivity in the cytoplasm of many meningiomatous elements
Smooth muscle actin, 630x

tous. Their biological behaviour varies from case to case and is often unpredictable because of a lack of association between the morphological features and the aspects characterising their biological aggressiveness.

PEC-omas are currently considered very heterogeneous tumours, since this label now includes neoplasms that were considered in the past to be very different forms, and that today have been reconsidered and reclassified[17, 30]. For example, lymphoangioleiomyomatosis of the lung, considered in the past as an amartoma of the interstitial tissues of this organ, is currently diagnosed as a PEC-oma on the basis of the presence of melanocytic antigens (HMB-45) in the cells[31]. Forms of clear cell monomorphous sarcomas with a perivascular arrangement histogenically deriving from adipose or muscular tissues are now classified as PEC-omas (after the discovery of similar immunohistochemical profiles)[14, 32].

Besides the basic antigen expression, represented by the presence of the melanocytic antigen HMB-45 and the smooth muscle actin, there are also a number of other antigens whose significance is still unknown.

Within this context, cases of PEC-oma have been reported with an antigenic expression also for the S-100 protein, for desmin and, albeit rarely, for the cytokeratines[33]. The characterising antigenic profile can also be inconsistent, as found in a case of clear cell leiomyosarcoma of the myometrium that tested negative for the melanocytic antigen HMB-45 in the primary tumour and positive for the metastases[34].

The PEC-omas have also undergone cytogenic investigation, which showed an upregulated expression of the D1 cyclines and a loss of heterozygosis of the TSC/1 and TSC/2 genes.

The presentation of this case is justified by the rareness of the finding and offers the opportunity for some reflections on the histogenesis of PEC-omas. In particular, we should consider the important complementary rôles of morphology, immunohistochemistry and electron microscopy in the diagnosis of PEC-oma. The question of whether immunohistochemical data play a more dominant rôle compared to the morphological and histogenic data remains open. Therefore, the antigenic profile of PEC-omas is decisive for the diagnosis even if the morphology, topography and the histogenesis might indicate otherwise.

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