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Gliomatosis peritonei as a natural experiment in tissue differentiation

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ABSTRACT ***Gliomatosis peritonei*** **(GP) is an unusual condition in which nodules of mature astroglia, often miliary and microscopic in size, are widespread in the peritoneum and abdominal lymph nodes. Its behaviour is benign and it is usually found in association with ovarian teratoma and rarely with teratomas of other organs. Implants grow rapidly and can remain unchanged for life. Astroglia is the main component, but other neural lineage elements and many other tissues can be found. Cells are mature but not terminal, since they express SOX2. Secondary associated lesions include: a) degenerative astrocytic changes, b) granulomatous and follicular chronic inflammatory changes, c) association with hormonally related changes, such as decidual peritoneal metaplasia and endometriosis and d) endothelial and adventitial vascular hyperplasia leading to haemoperitoneum. Two pathogenetic mechanisms are considered: direct seeding of immature neural cells from a primary tumour with subsequent differentiation and metaplasia from peritoneal stem cells.The former proposal is supported by clinicopathologic data such as ample cellular heterogeneity, coexistence of mature astroglia with neural blastema, as well as the shed keratin and hairs from the ovarian neoplasm. However, metaplasia is sustained by a heterozygosity pattern of GP nodules, identical to the normal tissue and different from the coexistent ovarian teratoma. GP would constitute a response to growth factors from teratoma or macrophages. While an implantative origin from ovarian teratoma remains in most cases a more probable mechanism, metaplasia from peritoneal stem cells would explain cases of GP which present a monomorphic astrocytic cell population.**

KEY WORDS: *gliomatosis peritonei, ovary, teratoma, ectopic glia, SOX2*

Introduction

Gliomatosis peritonei (GP) is an unusual condition consisting in the presence of multiple nodules of mature astrocytes in the serosal peritoneal surface of the abdominal cavity. Although its clinical picture of peritoneal spread is that of advanced stage neoplasia, its behaviour is almost invariably benign, since its differentiated cells lack proliferative activity (Fortt *et al.,* 1969; Nogales *et al.,* 1974; Robboy *et al.,* 1970).

The majority of cases of GP are associated with an immature ovarian teratoma and only rarely with mature teratomas (Dhingra *et al.,* 2007; Gocht *et al.,* 1995); albeit a rare phenomenon, it can occur in up to a fourth of all cases of ovarian immature teratoma. Although GP has been reported in association with isolated cases of teratomas of the stomach, liver and bladder (Karlo *et al.,* 2009; Torikai *et al.,* 2007; Yeo *et al.,* 2010), such exceptional cases do not really conform to the classic picture of miliary peritoneal spread of GP that occurs with ovarian teratoma; instead they are large, circumscribed masses more suggestive of usual-type metastases.

Traditionally, the association with a concomitant neoplasm has favoured the hypothesis of GP as a phenomenon of implantation and subsequent maturation of neural precursor cells detached from the primary tumour. However, in the female peritoneum, the presence of ectopic benign tissues such as serous tubal epithelium is extremely frequent. Exceptionally, numerous nodules of highly differentiated thyroid tissue may be found in the peritoneum; the so called benign strumosis (Karseladze *et al.,* 1994), which may occur in association with struma ovarii. Also, well differentiated Sertoli cell tumours can implant foci of benign immature Sertoli-cell tubules in the peritoneum (Onida *et al.,* 2010). The pathogenesis of these mature ectopic tissues is not clear and both mechanisms of direct seeding/differentiation from a primary tumour (Robboy *et al.,* 1970) and peritoneal metaplasia (Ferguson *et al.,* 2001) from stem cells have been proposed.

Abbreviations used in this paper: GP, gliomatosis peritonei.

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In this review we will focus on the clinical and histological features of GP, with special consideration of its histogenesis, which may include two alternative mechanisms.

Clinical features

GP affects a broad age range, from childhood to postmenopausal patients, with a peak in the second and third decades of life and only few instances above the age of sixty. Often occurring as an incidental finding during surgery for ovarian tumour or in second look operations after a diagnosis of teratoma, it is consistently associated with a unilateral solid tumour. GP may occur after capsular rupture during surgery or spontaneously. When oophorectomy alone is performed without accompanying salpingectomy, there is a high chance of rupturing the capsule at the ovarian pedicle at hilar level.

The overall prognosis of GP is excellent and chemotherapeutic treatment is unnecessary. Long follow-up studies have demonstrated its benign course (Fortt *et al.,* 1969; Robboy *et al.,* 1970). A recent study comparing ovarian immature teratomas with and without GP demonstrated a similar overall good survival but with a higher incidence of early recurrences in the cases associated with GP (Mann *et al.,* 2008; Yoon *et al.,* 2012). Occasionally, GP may precede highly malignant neuroectodermal tumours (Dadmanesh *et al.,* 1997; Shefren *et al.,* 1991; Trabelsi *et al.,* 2002). Cases from the older literature reporting early malignant behaviour may correspond to recurrences of incompletely sampled peritoneal disease, with foci of immature tissue not identified at the time of surgery.

Implants can grow rapidly. In one instance, they were detected in a second look operation performed only one month after oophorectomy for immature teratoma (Nogales *et al.,* 1974). In rare instances, such as another of our cases, PG can be an incidental autopsy finding of asymptomatic residual disease in elderly patients who had had ovarian teratoma in their youth.

Among serum markers, CA125 levels are elevated in GP (Yoon *et al.,* 2012) and some authors (Bahari *et al.,* 1980; de Graaff *et al.,* 1980; Hokama *et al.,* 1991) have also reported elevated alpha-fetoprotein levels, possibly related to endodermal elements present in the immature teratoma deposits.

Pathology findings

Primary teratoma

GP occurs in association with a unilateral solid ovarian teratoma. Histologically the primary tumour shows tissues with a variable degree of immaturity. However, the predominant tissue is of neural type and comprises large amounts of well differentiated glial tissue with other neuroectodermal components. Other frequent non-neurological constituents are skin, developing teeth, gastrointestinal derivatives although, eventually, any imaginable tissue can be found (Nogales *et al.,* 2003).

Histological tumour grading of teratomas is a valuable tool for predicting their behaviour (Nogales *et al.,* 1976; Norris *et al.,* 1976; Thurlbeck *et al.,* 1960). It is performed by a subjective, semiquantitative analysis of the relative number and atypicality of immature neural tissues present in the neoplasm such as neuroepithelial tubules and neural blastema. This is accomplished either by the traditional approach of assigning 4 grades ranging from fully mature (grade 0) to highly immature (grade 3) or by establishing a two tier system into low grade and high grade tumours (O'Connor *et al.,* 1994). Ovarian neoplasms associated with GP are most frequently of grade 1 or 2 and only rarely may correspond to grades 0 (fully mature) or 3 (highly immature). When found in association with grade 0 solid teratomas, the tumour warrants a more extensive tissue sampling in order to exclude any immature foci. Evaluation of immaturity can be enhanced by the immunohistochemical analysis of pluripotency markers such as SALL4 and SOX2 which are highly sensitive in the identification of neural immature cells (Nogales *et al.,* 2012).

An interesting aspect of ovarian immature teratoma is the concomitant vascular response present in association with neural tissues. There is an extensive endothelial proliferation of vessels, similar to that occurring in tumours of the central nervous system, originating as a response to angiogenic factors secreted by immature neural elements (Baker *et al.,* 2002; Nogales *et al.,* 2002;

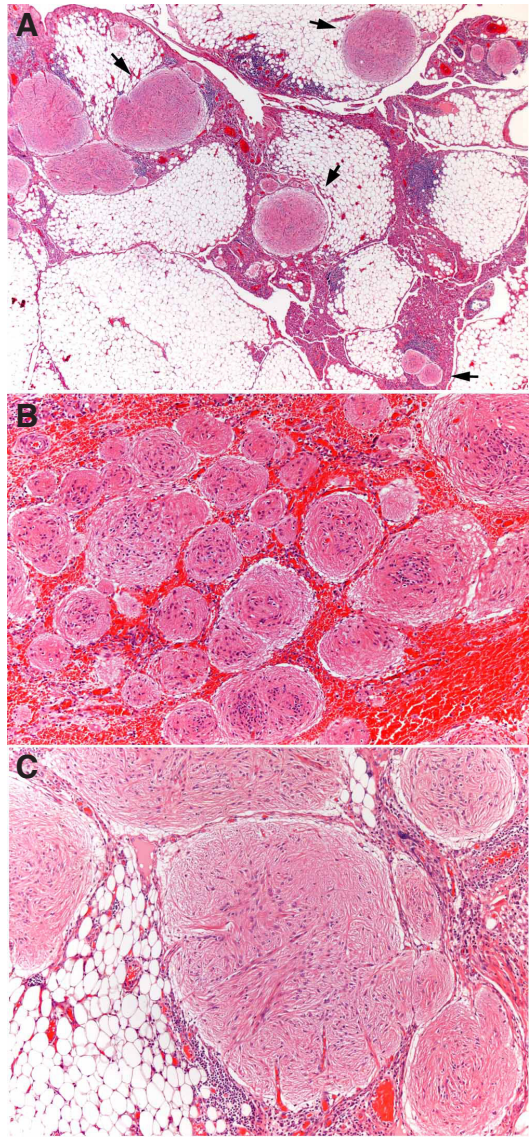

Fig. 1. Characteristic appearance of *Gliomatosis peritonei* (GP) at low power. *Multiple astrocytic nodules (arrows) are scattered throughout the omental surface and underlying fatty tissue* **(A)**. *Glial nodules are surrounded by haemorrhage* **(B)**. *Higher magnification* **(C)** *reveals uniform, mature glial cells set in a fibrillary matrix.*

Nogales *et al.,* 1983; Nogales *et al.,* 1974). Only on rare occasions a secondary, highly malignant neural tumour, such as primitive neuroectodermal tumour (PNET) may develop from the stem cells present in ovarian immature teratoma. In these cases, metastases are always of high grade (Morovic *et al.,* 2008).

Gliomatosis peritonei

Appears as miliary deposits scattered throughout the peritoneum involving every serosal surface including recesses, cul-de-sac, intestinal surface, etc. In a few cases the coexistence of adhesions due to endometriosis may give it a more complex appearance. Haemorrhage can be present in the nodules. Surgical sampling should be as extensive as possible in order to evaluate fully the immaturity of the peritoneal deposits. Chemotherapy will depend on grading of GP, being indicated for high grades and not administered in grade 0 implants.

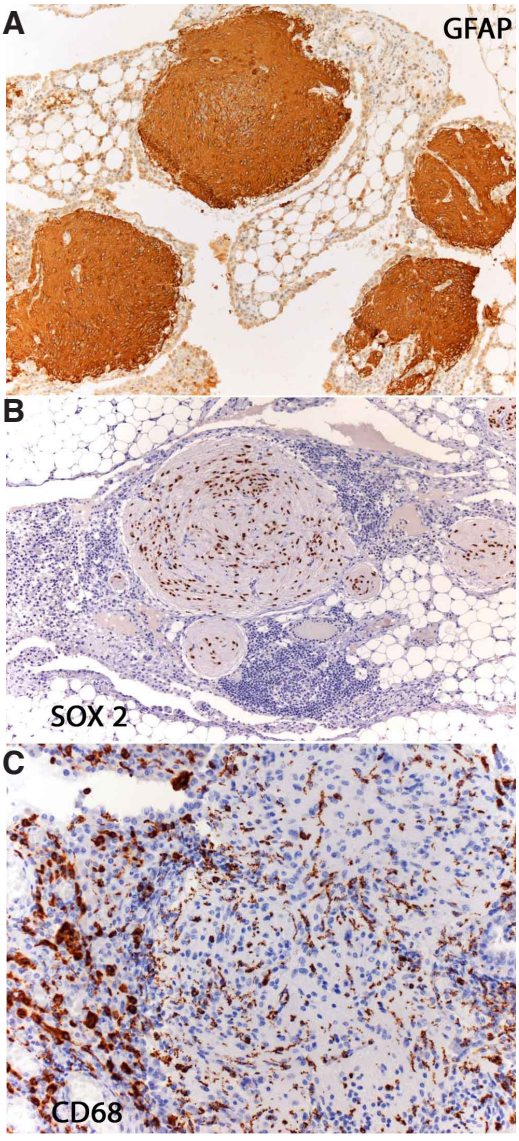

Fig. 2. Immunohistochemistry of *Gliomatosis peritonei* (GP). *Nodules are intensely positive for glial fibrillary acidic protein* **(A)**. *Nuclei, despite a mature appearance, express SOX2* **(B)**. *CD68 stains macrophages and intranodular stellate cells identical to microglia* **(C)**.

Macroscopically, GP appears as white or yellow nodules of variable size ranging from 1mm to 1cm and can be difficult to visualize. Indeed, they are often only microscopic and sometimes are an incidental finding in specimens from an omentectomy performed at the time of oophorectomy (Nogales *et al.,* 1974). True GP should be differentiated from large, discrete nodules of peritoneal metastases.

Microscopically, nodules are scattered through the peritoneum (Figs 1A,B) and composed of a glial cell population with mature features, minimal atypia and only rare mitoses. The predominant cell types are fibrous astrocytes (Fig 1C) staining for glial fibrillary acidic protein (Fig 2A). Their nuclei do not express pluripotency gene SALL4 protein, which is present in immature neural tissue (Ma Y.2012, Nogales *et al.,* 2012) but are positive for SOX2 (Fig 2B), a pluripotency transcription factor involved in neurogenesis (Noisa *et al.,* 2012), indicating that cells are mature but not terminally differentiated cells. Ultrastructurally, presence of other neural lineages such as oligodendroglia, ependymal, melanocytic and even neurons is demonstrated (Gonzalez-Campora *et al.,* 1979). Immunohistochemically, the NeuN neuronal nuclear antibody often shows scattered positive neuronal cells. Additionally, we have been able to detect the presence of CD68 positive microglia-like cells in the GP nodules (Fig 2C).

There are instances where the coexistence of foci of immature neuroepithelium with a mature glia is indicative of its differentiation from immature precursors (Fig 3A). Other non-neural tissue

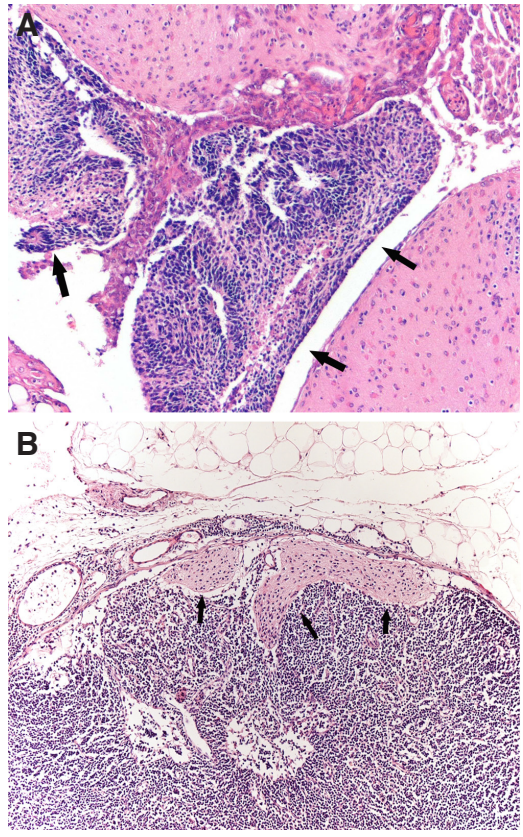

Fig. 3. Mature glial nodules *(gliomatosis peritonei) may coexist with foci of immature neural tissue exhibiting neuroepithelial tubules (arrows)* **(A)**. *Gliomatosis peritonei (GP) (arrow) is present in the marginal sinus of an abdominal lymph node* **(B)**.

components such as epidermis, cartilage, respiratory and digestive tract epithelia may also be present in the nodules.

GP involvement of lymph nodes (Heifetz *et al.,* 1998; Mann *et al.,* 2008; Muller *et al.,* 2002) is often an incidental finding in abdominal lymphadenectomy specimens, occurring in the marginal sinus (Fig 3B).

Secondary associated lesions in GP may include the following:

1. Degenerative changes in the GP astrocytes such as Rosenthal fibres, granular gemistocytes (Fig 4A), corpora amylacea etc.
2. Inflammatory changes: Chronic inflammation, frequently with follicular formation, is a common phenomenon around GP nodules (Fig 4B). Granulomatous reaction of foreign-body type occurs in relationship with keratin-rich desquamated epidermis or hairs (Fig 4C,D). In cases of long standing GP, a chronic macrophagic reaction can practically overgrow and erase the glial component.
3. Hormonal changes such as decidual transformation of mesothelium can also arise in the neighbouring peritoneum in cases of GP occurring during pregnancy (Fig 4E).
4. Vascular hyperplasia occurs in the vicinity of the nodules exhibiting a complex glomeruloid appeareance due to the proliferation of endothelial and adventitial vascular cells (Nogales *et al.,* 2002) (Fig 4F). These fragile, irregular vessels can be the source of hemoperitoneum.
5. Post-chemotherapy changes reveal degenerative nuclei in astrocytic cells (Fig 4G).
6. Endometriosis. Foci of endometrial tissue displaying both glands and stroma can coexist in the ovarian surface and peritoneum, where isolated glands are surrounded by GP. However, no cases of coexistence of leiomyomatosis peritonealis disseminata or endosalpingiosis/endocervicosis have been reported in GP (Fig 4H).

Pathogenesis

It is by no means clear. Two alternative mechanisms of differentiation have been proposed:

Peritoneal implantation

The aetiology of GP has been related, since its initial description (Robboy *et al.,* 1970), to implantation of immature neural tissue into the peritoneum subsequent to capsular rupture, either spontaneous or surgical. Thus there would be seeding of immature precursors that eventually differentiate into benign, terminally differentiated cells, including glia.

Data supporting this possibility include the following:

a) GP nodules do not only contain glia, but several other neurogenic lines (Gonzalez-Campora *et al.,* 1979) and other tissues such as skin, gut, cartilage etc. This ample range of differentiation is characteristic of teratoma. Furthermore, immature neuroepithelial tubules may coexist with other neural cell lines

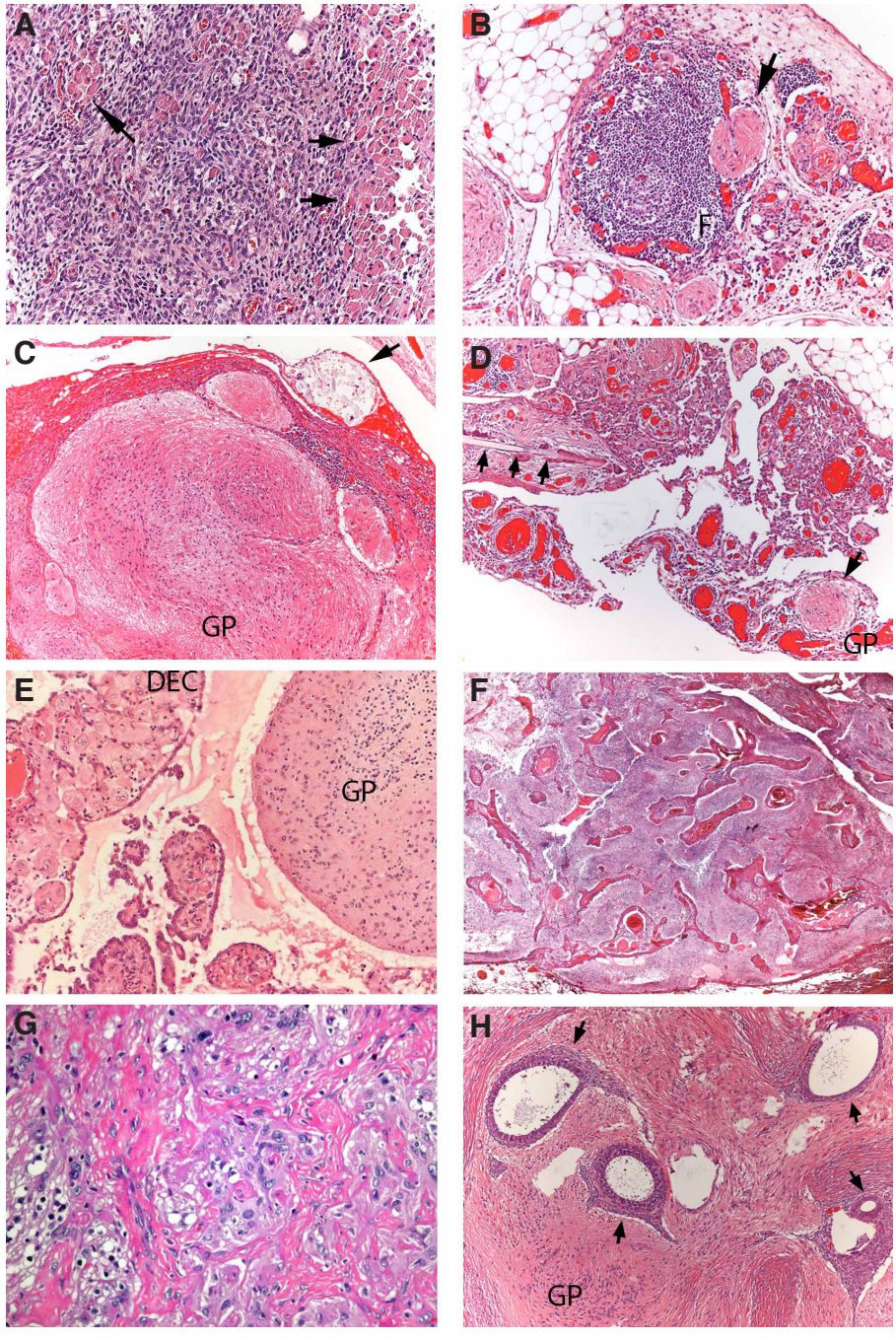

Fig. 4. Secondary changes in *Gliomatosis peritonei* (GP). *Presence of granular gemistocytes* **(A)**. *Chronic lymphocytic, follicular (F) infiltration around a GP nodule (arrow)* **(B)**. *Coexistence of GP with keratin peritoneal deposits (arrow)* **(C)**. *A GP nodule coexists with teratomatous hairs from ovarian primary (arrows)* **(D)**. *Decidual peritoneal change (DEC) in a pregnant patient coexists with GP* **(E)**. *Florid vascular hyperplasia in a case associated with haemoperitoneum* **(F)**. *Postchemotherapy glial atypia* **(G)**. *Coexistence of GP with numerous embedded foci of ectopic endometrium (arrows)* **(H)**.

(Fig. 3A). All those features would indicate a teratoid maturation from embryonal, immature precursors from the ovarian tumour. Local differentiation would occur either spontaneously or induced by platin-based chemotherapy (Gibas *et al.,* 1993; Kane *et al.,* 2009; Yoon *et al.,* 2012). Although most cases of implanted glial tissue mature spontaneously, chemotherapeutic conversion of neural immature cells into benign ones is the proposed mechanism for cases of growing teratoma syndrome associated with GP (Hsieh *et al.,* 2009; Umekawa *et al.,* 2005).

b) Shed keratin scales and hairs from the primary ovarian teratoma (Figs 4C,D) are often associated with GP, representing a gross but evident marker of its origin in the ovary and its subsequent transport into the peritoneum through the capsule.

c) Cases showing lymph node involvement (Figs 3B) by foci mature glial, even in the absence of a peritoneal lesion (El Shafie *et al.,* 1984; Heifetz *et al.,* 1998; Perrone *et al.,* 1986), would indicate a lymphatic transport of neural immature precursors that would eventually undergo full differentiation in the lymph nodes.

d) There are rare cases of GP associated with ventriculo-peritoneal shunts which would constitute a natural experiment of the implantative capacity into the peritoneum of glial cells present in the cerebrospinal fluid (Hill *et al.,* 2000; Lobotesis *et al.,* 2009; Lovell *et al.,* 1989).

e) Some ovarian tumours such as struma ovarii (Karseladze *et al.,* 1994) and well differentiated Sertoli cell neoplasms (Onida *et al.,* 2010), are capable of producing highly differentiated nodular and miliary implantations in the peritoneum after tumour rupture or manipulation.

Multifocal peritoneal metaplasia induced by growth factors

In the last decade, genetic studies analysing multiple microsatellite markers in microdissected GP implants (Best *et al.,* 2004; Ferguson *et al.,* 2001; Kwan *et al.,* 2004) have demonstrated that they have a heterozygosity pattern identical to the normal tissue and different from the coexistent ovarian teratoma, which is homozygous at the same loci. Although performed in only a few cases, these findings would imply a different genetic identity for the ovarian tumour and GP and thus challenge the classical implantative mechanism. This would favour the possibility of a metaplastic phenomenon from pluripotent subperitoneal cells, which would be a response to growth factors originating either from the coexistent teratoma (Ferguson *et al.,* 2001), local macrophages (Gocht *et al.,* 1995) or in the cerebrospinal fluid of ventriculoperitoneal shunts (Ferguson *et al.,* 2001).

This would parallel a mechanism analogous to that giving rise to monoclonal peritoneal proliferations of such diverse tissues as smooth muscle (Guarch *et al.,* 2001; Nogales *et al.,* 1978) and epithelia such as endometrial (Clement *et al.,* 2007), tubal- (Dallenbach-Hellweg *et al.,* 1995; Donne *et al.,* 1998) and endocervical (Liu *et al.,* 2009), which would originate in stem cells with a capacity to develop into Müllerian cell lines under the influence of hormonal growth factors. This has been aptly called the secondary Müllerian system (Lauchlan *et al.,* 1994), which is not restricted to the peritoneum, but also present in the urinary bladder (Donne *et al.,* 1998), ureter (Nogales *et al.,* 1999), pleura and even in the abdominal and axillary lymph nodes (Stolnicu *et al.,* 2011).

The proposed local metaplastic peritoneal origin of GP would imply that stem cells would also be endowed with a further capacity to develop into non Müllerian lineages such as astroglia. The occasional association of PG and endometriosis (Fig. 4H) (Albukerk *et al.,* 1979; Alexander *et al.,* 2011; Bassler *et al.,* 1982; Calder *et al.,* 1994; Dworak *et al.,* 1988; Killeen *et al.,* 1997) would give partial support to this assumption. Endometriosis is a common condition currently considered to be of metaplastic origin in most cases (Clement *et al.,* 2007). However, since pathogenetically related leiomyomatosis peritonealis disseminata, endosalpingiosis or endocervicosis have not been reported in association with GP, the association of endometriosis with GP may be coincidental, as endometriosis is a very common condition.

Taking into account both possibilities it would seem that an implantative origin from ovarian teratoma pluripotent precursors remains in most cases the more probable mechanism, although a metaplastic transformation from peritoneal stem cells under adequate growth factor stimulation is conceivable. We believe that this latter pathway would be restricted, however, to cases of GP that have a monotonous, monomorphic astroglial cell population, which would represent a selective cell lineage differentiation.

Author's roles

Francisco F. Nogales designed the study and participated in the analysis, execution and manuscript drafting and critical discussion. Isabel Dulcey retrieved archive material, performed the immunohistochemical and bibliographical analysis and participated in the manuscript drafting and critical discussion. Ovidiu Preda was responsible for the illustrations and immunohistochemistry.

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