

## OVARIAN SMALL CELL CARCINOMA OF HYPERCALCEMIC TYPE – EVIDENCE OF GERMLINE ORIGIN AND *SMARCA4* GENE INACTIVATION. A PILOT STUDY

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*In memory of Robert Edward Scully...*

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Ovarian tumors from two patients, compatible by histological and immunohistochemical criteria with small cell carcinoma of hypercalcemic type (SCCHT) (WT1+, EMA dispersed+, synaptophysin+ or dispersed+), were extensively sampled in order to find clues to their histogenesis. Subsequently, small foci of immature teratoma were found in both of them (in 1/122 and in 3/80 tumor sections). In one case, microfoci of yolk sac tumor were also present within the teratoma area as well as in the background of the small cell tumor population – in the primary tumor and in omental metastasis. We found a resemblance of the microscopic patterns of SCCHT and atypical teratoid/rhabdoid tumor (AT/RT) of the central nervous system, and this prompted us to evaluate INI-1 and SMARCA4 immunohistochemical expression, because their alternative loss is regarded as a molecular hallmark of AT/RT. INI-1 expression was retained, while that of SMARCA4 was lost. We therefore analyzed tumor DNA by PCR amplification and sequencing for mutations in the *SMARCA4* gene (NG\_011556.1), which were identified in both tumors (c.2184\_2206del; nonsense c.3277C>T – both in one tumor; nonsense c.3760G>T in another tumor). These data suggest that SCCHT is most likely an embryonal tumor originating from immature teratoma and related to malignant rhabdoid tumor. Further analyses are necessary to determine whether the tumors diagnosed as SCCHT constitute a homogeneous group or represent more than one entity.

**Key words:** small cell carcinoma of hypercalcemic type, immature teratoma, embryonal tumor, atypical teratoid/rhabdoid tumor, rhabdoid tumor, ovary.

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## Introduction

Ovarian small cell carcinoma of hypercalcemic type (SCCHT) is a rare and highly malignant neoplasm affecting young females. In the largest published series of 150 cases, patients ranged from 9 to 43 years old (median 24), with a peak in the third decade [1]. Clinically the tumor is characterized by a poor response to available chemotherapies and generally short progression-free survival. Overall survival of affected patients depends on clinical stage: it ranges from 5 months to several years for FIGO stage I, and 2-23 months for FIGO stage III disease [2].

According to its first description by Dickersin, Kline and Scully [3], SCCHT is characterized by diffuse proliferation of small, round to oval, rather discohesive undifferentiated cells, forming nests and cords that are variably punctuated by pseudofollicles. Cells with abundant eosinophilic cytoplasm, sometimes with eccentrically placed nuclei causing a rhabdoid appearance, can be appreciated in about one third of the tumors. The paradoxical name of the large cell variant of small cell carcinoma of hypercalcemic type was given for tumors with a significant proportion of large cells [1, 3].

Despite many years of examination of such tumors, little is known concerning their histogenesis and molecular background [1, 4-6]. Identification of the nature and underlying molecular changes may ultimately lead to better therapeutic solutions.

Herein we present evidence of the germline origin of two SCCHT having *SMARCA4* gene inactivation. The similarity to malignant rhabdoid tumor (MRT) and atypical teratoid/rhabdoid tumor (AT/RT) of infancy and childhood is brought to light.

## Material and methods

### Patients and tumors

The study was performed on two formalin-fixed ovarian tumors that were available in the year 2013 for prospective evaluation in the Department of Pathology of the Institute of Oncology in Warsaw.

**Case 1 (PJK1182).** A 35-year-old patient, gravida 5 para 1, underwent cesarean section in the 33<sup>rd</sup> week of pregnancy due to several complications of pregnancy. A right ovarian tumor was detected during the surgery. The tumor measured 16 × 11 × 7.5 cm. On cut section it was solid, grey-beige, with necrosis and hemorrhages; the capsule was ruptured. Subsequent staging laparotomy (total abdominal hysterectomy [TAH] and bilateral salpingo-oophorectomy, omentectomy and lymphadenectomy) revealed FIGO stage IIIB neoplasm.

**Case 2 (PJK1233).** The other patient (27 years old, gravida 0) underwent left ovarian tumor removal at another hospital and received 4 cycles of cisplatin and etoposide chemotherapy. The patient reported a fulminant growth of the tumor, from 8 cm at the time of ultra-

sonographic diagnosis to 16 cm two weeks later. The tumor of the left ovary measured 16 × 8 × 8 cm; it was solid and cystic, grey-white, necrotic and involved the tumor capsule. At that time omental biopsy and salpinx were unremarkable (FIGO IC). Nineteen months later the patient underwent TAH and right salpingo-oophorectomy, omentectomy, sigmoidectomy and splenectomy because of disseminated SCCHT (FIGO stage IIIC). A tumor of the right ovary measured 8 × 5 × 3.5 cm and was grey-white, solid and firm.

### Immunohistochemical analysis

Immunohistochemical staining was performed on paraffin-embedded material after heat-induced epitope retrieval (HIER). For *SMARCA4* evaluation we used a mouse monoclonal IgG1 antibody (Brg-1 clone G-7, dilution 1/250, Santa Cruz Biotechnology, Santa Cruz, CA, USA) raised against amino acids 209-296 near the N-terminus of human *SMARCA4* protein [7]. The antigen was retrieved by heating the sections in 0.01 M citrate buffer (pH 6.0) at 700 W in a microwave oven. Non-specific tissue and endogenous peroxidase reactivities were blocked with 10% BSA and 3% H<sub>2</sub>O<sub>2</sub>, respectively. The sections were incubated with the primary antibody overnight, at 4°C. Biotinylated secondary goat anti-mouse IgG (dilution 1/1500), peroxidase-conjugated streptavidin (dilution 1/500) (all from Immunotech, Marseille, France), and DAB were used as a detection system. Normal stromal and endothelial cells served as internal positive controls, while sections of human breast and ovarian carcinoma served as external positive controls.

For detection of other proteins the Dako EnVision FLEX detection system was used. The following primary antibodies were applied: monoclonal anti-INI1 (clone MRQ-27, dilution 1/100, Cell Marque, Rocklin, CA, USA), ready-to-use anti-WT1 (clone 6F-H2), -EMA, -TP53, -synaptophysin, -cytokeratin (clone AE1/AE3), -PLAP, and polyclonal anti-chromogranin A and -AFP (Dako, Glostrup, Denmark). The antigens were retrieved in EnVision Flex Target Retrieval Solution (pH 9.0) at 97°C. EnVision FLEX/HRP detection reagent was used as a detection system (Dako, Glostrup, Denmark). All immunostained sections were counterstained with hematoxylin.

### Analysis of the *SMARCA4* gene mutations

Genomic DNA was isolated from formalin-fixed paraffin-embedded sections using the QIAamp DNA Extraction Kit (Qiagen, Germany) following the kit's instructions.

Coding sequences of the *SMARCA4* gene with intron/exon boundaries were PCR-amplified and sequenced as previously described [8]. Some primer sequences were taken from a publication by Medina *et al.* [9], while others were designed using the free

**Table I.** PCR and sequencing primers for exons with mutations detected

EXON	FORWARD PRIMER	REVERSE PRIMER
15*	TTACCCGGCACCTCCATCTC	ACCTGGGAACACCTGCAC
24*	CGCCTTCTCTCCTGCCTCCTC	AGCTTCTGTGGCAGCCACAA
26b	CTCAACGTGGACCAGAAGGT	TCAGCCCACACTCCCTTTAC

\*Primers based on published sequences [9]

Primer3 software and the *SMARCA4* genomic sequence [GenBank: NG\_011556.1]. Altogether we used 21 primer pairs for 21 (out of 35) exons examined (3, 5, 8, 9, 12-21, 23-26, 31, 32, 35). The PCR and sequencing primers used for the analysis of exons in which mutations have been detected are listed in Table I. Thermal cycling conditions are available on request. DNA was sequenced with ABI dye terminator sequencing kit (v.3.1) according to the manufacturer's recommendations in an ABI PRISM 3100 sequencer (Life Technologies, Foster City, USA).

## Results

### Light microscopic findings

Both ovarian tumors were compatible with the histological pattern of small cell carcinoma of hypercalcemic type [3]. The predominant population was that of small undifferentiated ovoid cells (Figs. 1A-D, 2A-C). There were also foci of large cells with eosinophilic cytoplasm, with or without eccentrically displaced nuclei (rhabdoid features) (Figs. 1D, E); in some areas rhabdoid features were present in medium-sized cells in both tumors; however, they were more frequent in tumor 1; hyalinized foci with a signet-ring appearance of tumor cells were also seen (Fig. 1F). The architecture was heterogeneous and disordered – with nests and cords of cells, sometimes embedded in a myxoid stroma (Figs. 1B, C, 2C, D). Solid areas were variably punctuated by pseudofollicles (Figs. 1A, 2A); some foci suggested that pseudofollicles arose by disintegration of solid structures (Fig. 2B).

In tumor 1, the first series of tumor sections (n = 22) showed several benign-appearing (or with only a minor degree of atypia) epithelial glandular structures of mixed histology (mucinous, clear cell, with squamous

metaplasia: WT1–, CK7+, CK20+), focally embedded in a dense fibrous stroma, suggesting teratomatous origin (Figs. 1G1, H2; 4G). Within the small cell tumor population there were some distinct malignant glandular structures covered by cells compatible with adjacent small tumor cells, showing also mucinous differentiation (Figs. 1B, G2). One hundred additional sections were taken and in one of them a small (0.2 cm) immature neuroepithelial focus was found (Fig. 3A). Deeper sections of the teratoma area revealed highly atypical and mitotically active immature teratoma cells infiltrated by SCCHT cells.

Tumor 2 contained microfoci of yolk sac tumor (YST, Figs. 2E, 4A-D); they were present in the right ovarian tumor removed during the second surgery. Altogether there were 5 microfoci of YST (AFP+, Fig. 2G) in a background of small tumor cells (in 5 different tumor fragments) – one microfocus was present in an omental metastasis. Additional sections were taken and an area of immature teratoma measuring approximately 1 × 1 cm was found in 3 of 80 sections analysed (Fig. 3C; 4F, H). The teratoma consisted of easily recognisable immature neuroepithelium (Fig. 3C), some undifferentiated areas and foci of squamous epithelium, and was admixed with yolk sac tumor (Fig. 4C-D). The teratoma showed infiltration by small tumor cells.

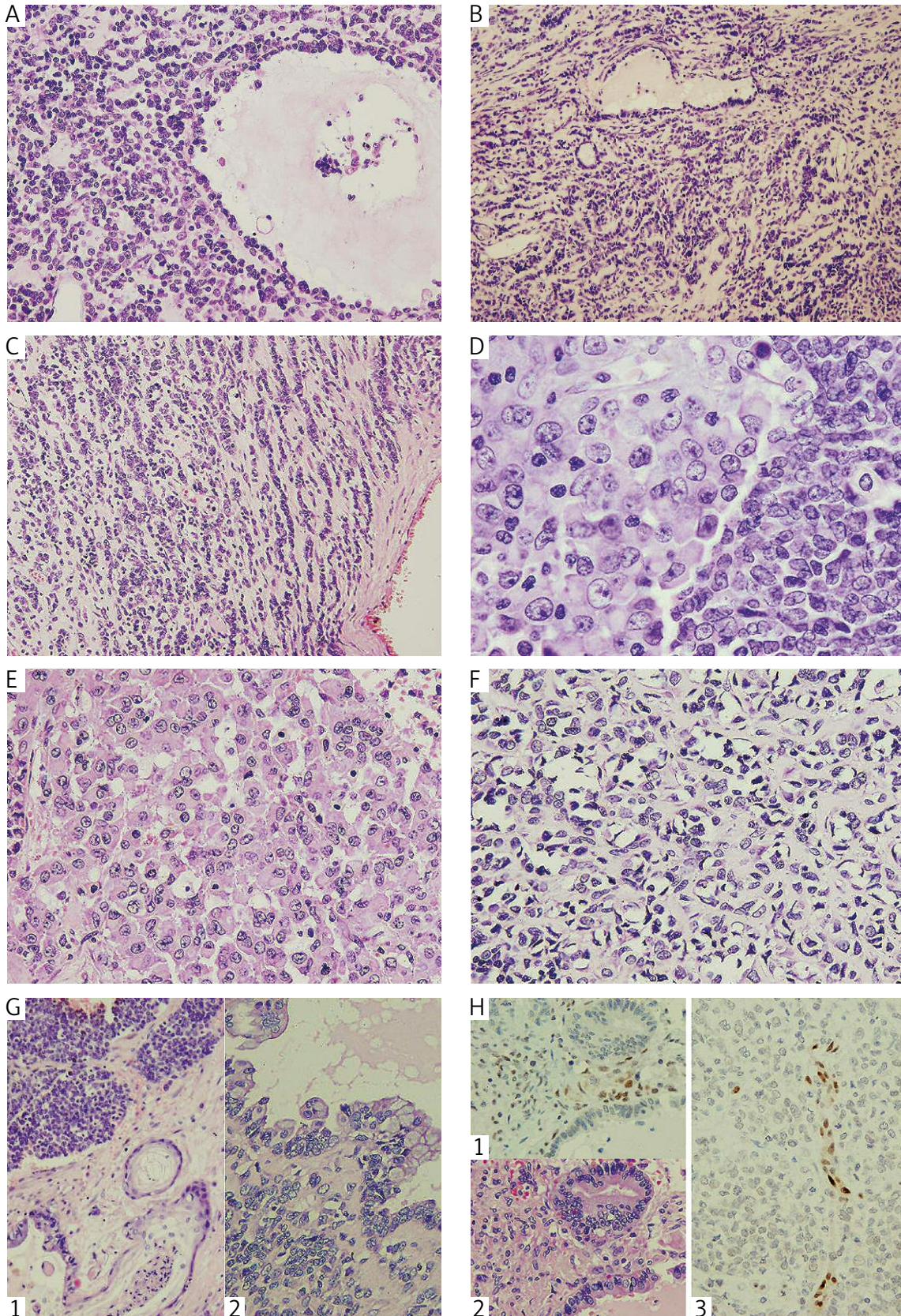
### Immunohistochemical findings

Both tumors showed strong nuclear expression of WT1, heterogeneous nuclear expression of TP53, and dispersed positivity for EMA and cytokeratin AE1/AE3 (in tumor 2 the latter was observed in single cells). Expression of synaptophysin was diffuse in tumor 1 and present in single cells in tumor 2; both tumors were negative for chromogranin A. INI-1 nuclear staining was strong and diffuse in both. YST structures were

**Table II.** SMARCA4 mutations found in the two ovarian tumors studied

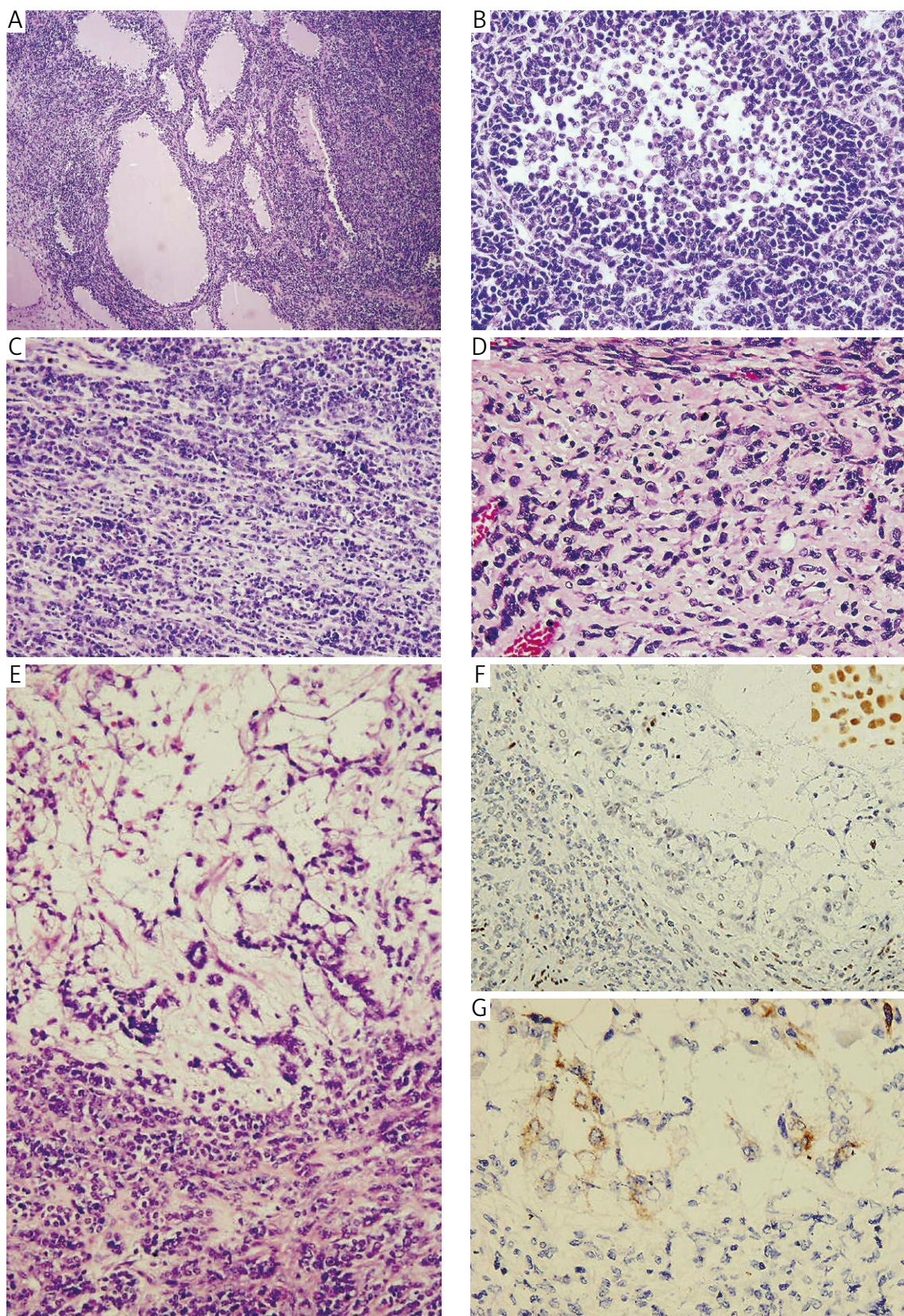
PROBAND NO.	AGE	FIGO	SMARCA4 EXPRESSION	SMARCA4 MUTATION
PJK1182	35	IIIB	negative	exon 26 c.3760G>T; p.(Glu1254Ter)
PJK1233	27	IC	negative	exon 15 c.2184_2206del, p.(Gln729fs) exon 24 c.3277C>T; p.(Arg1093Ter)





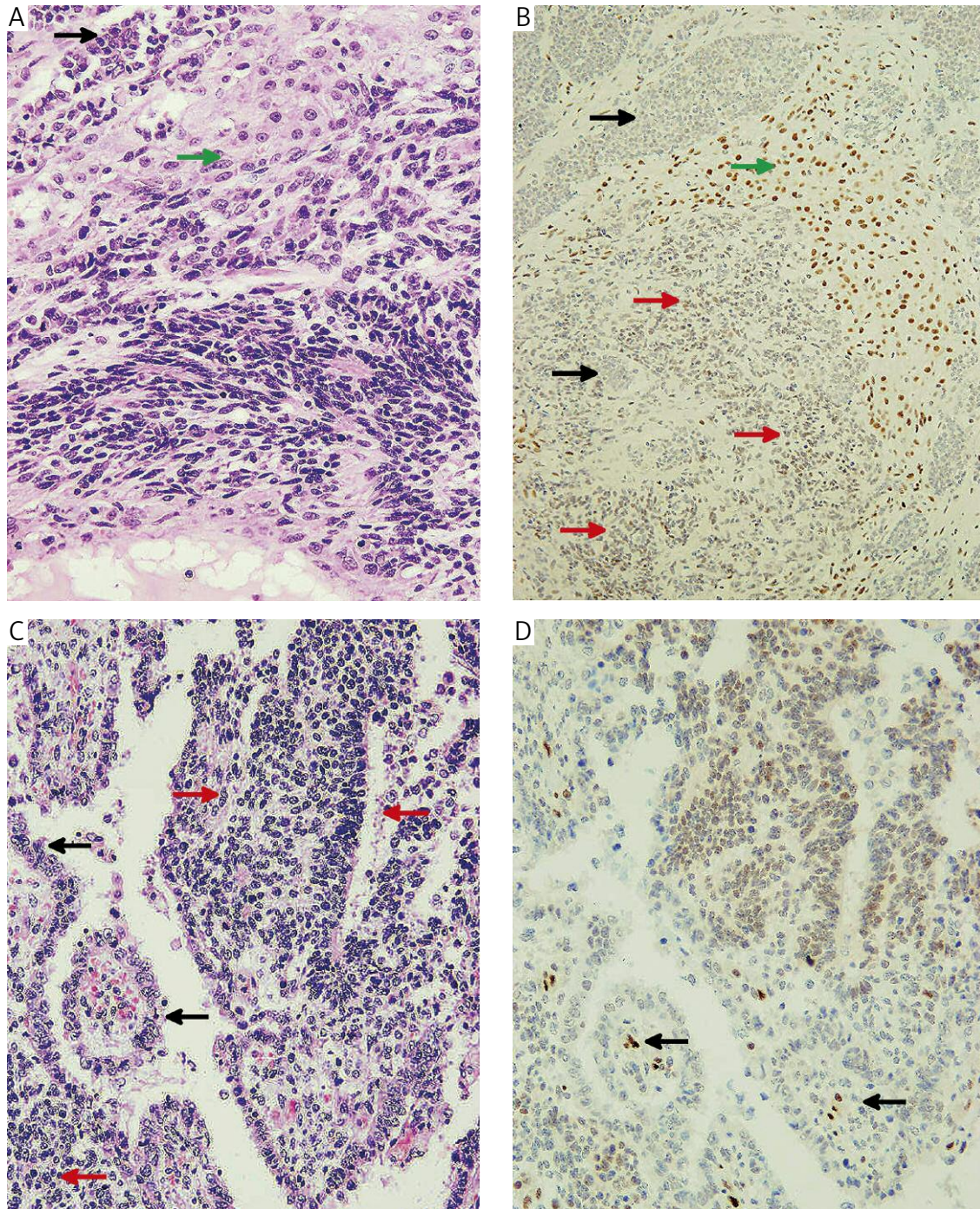
**Fig. 1.** Ovarian small cell carcinoma (tumor 1, PJK1182): histological pattern (HE staining) and SMARCA4 expression (hematoxylin counterstain): A) A follicle-like structure (100×). B) Disordered architecture with malignant glandular structure formed by tumor cells (100×). C) Infiltration in cords (100×). D) Large (to the left) and small tumor cells (to the right) (400×). E) Large cells, some with rhabdoid features (200×). F) Hyalinized stroma with vacuolated, signet ring cells (200×). G1) Squamous metaplasia in a glandular structure in the vicinity of small tumor cells (100×). G2) Mucinous differentiation in a glandular structure covered by highly malignant tumor cells (200×). H) Loss of SMARCA4 expression (H1) in benign glandular structures (H2) and small tumor cells (H3) (200×); strong SMARCA4 expression in the endothelium and some stromal cells





**Fig. 2.** Ovarian small cell carcinoma (tumor 2, PJK1233): histological pattern (HE staining), SMARCA4 and AFP expression (hematoxylin counterstain): A) Several follicle-like spaces in a background of small cell tumor (40×). B) Discohesive cells in a solid focus, apparently forming a follicle (200×). C) Disordered heterogeneous architecture (100×). D) Tumor cells in a myxoid stroma (200×). E) Yolk sac tumor focus in a background of SCCHT cells (100×). F) SMARCA4 expression in the area presented in E): negative SMARCA4 staining in the YST and SCCHT; positive internal controls (endothelium and stromal cells) (100×); the insert shows strong SMARCA4 expression in a serous ovarian cancer. G) AFP expression in the area presented in E): positive staining in the YST and negativity of SCCHT cells (200×)





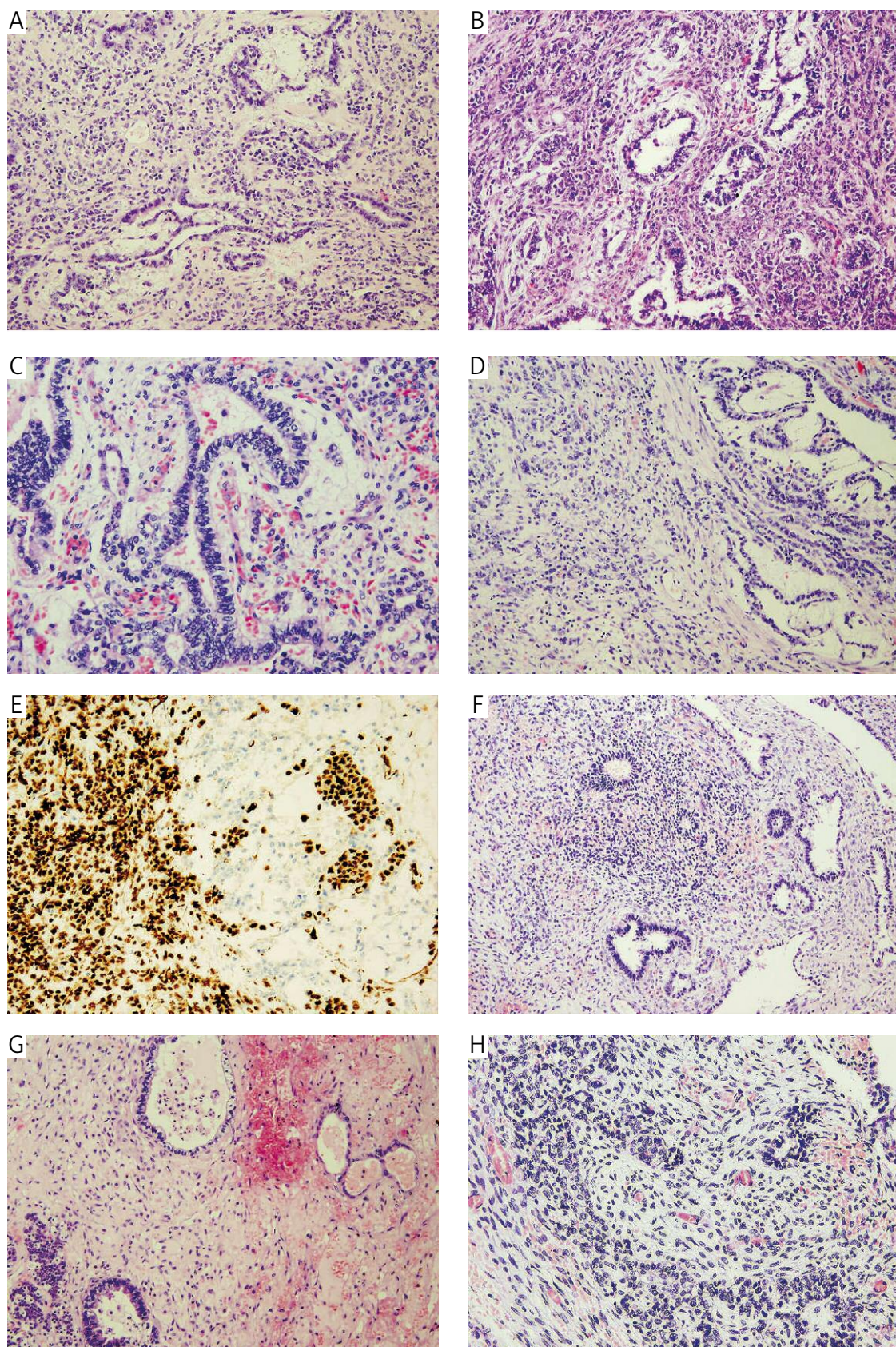
**Fig. 3.** Teratomatous structures detected in two ovarian small cell carcinomas of hypercalcemic type: A) Tumor 1, immature neuroepithelium in the lower half of the picture, with adjacent luteinized ovarian stromal cells (green arrow), and SCCHT cells in the upper left corner (black arrow) (HE,  $\times 200$ ). B) SMARCA4 expression in the area shown in A. Strong expression in luteinized and other stromal cells (green arrow), negative SCCHT cells (black arrows) and diminished expression in immature teratoma area (red arrows) (hematoxylin counterstain,  $\times 100$ ). C) Yolk sac tumor structure (black arrows, AFP+, PLAP-) and immature neuroepithelium (red arrows) (HE,  $\times 200$ ). D) SMARCA4 expression in the area presented in C: negative SMARCA4 staining in the YST cells, strong expression in the endothelium and some stromal cells (black arrows) and diminished expression in the neuroepithelial structure (hematoxylin counterstain,  $\times 200$ )

negative for WT1 protein (Fig. 4E) and positive for cytokeratin – in contrast to SSCHT cells. PLAP staining was not observed.

SMARCA4 expression was lost in both tumors (they were predominantly negative with some foci showing

barely visible nuclear staining), while it was positive in the endothelium and stromal cells (Figs. 1H3, 2F, 3B). The glands in tumor 1 were also negative (Fig. 1H1), while the immature teratoma had diminished expression of SMARCA4 compared with adjacent stromal cells





**Fig. 4.** Germ cell tumor elements found in the two SCGCT studied: histological pattern (HE staining) and WT1 expression (hematoxylin counterstain): A, B) Yolk sac tumor foci in a background of the SCGCT (100×). C, D) Yolk sac tumor structures in the teratoma area (AFP+, C: 100×; D: 100×); E) WT1 expression in the nuclei of the SCGCT and negativity of the YST tumor cells (on the right) (200×). F, H) Immature teratoma foci in the tumor 2 (F: 40×; H: 100×). G) Glandular structures in a fibrous stroma in the tumor 1 (100×)



(Fig. 3B). In tumor 2, the focus of immature teratoma showed heterogeneous expression of SMARCA4 protein: from negative to moderate, but generally weaker than non-neoplastic cells (Fig. 3D). Yolk sac tumor structures were negative or showed trace nuclear staining (Fig. 2F, 3D).

### Mutations in the *SMARCA4* gene

Analysis of most of the coding sequence of the *SMARCA4* gene revealed the presence of alterations in both tumors. In tumor 1 there was a single nonsense mutation in exon 26 that resulted in a premature stop codon (p.Glu1254Ter). In tumor 2 two nonsense alterations were found: a 23 bp deletion in exon 15 that resulted in p.(Leu729fs) and created a premature stop codon at position 732, and a substitution in codon 1093 (exon 24) which changed arginine to a termination codon (Table II). It may be expected that due to both nonsense alterations the SMARCA4 protein was shortened and devoid of its C-terminal fragment.

### Discussion

This study shows evidence of “germ cell tumor” origin of two ovarian SCCHT. The histogenesis of this tumor has been widely discussed starting from its first description by Dickersin *et al.* [3], and germline, epithelial and sex-cord origins have been considered [1, 3-5, 10]. The presence of teratomatous structures would have helped to solve the question; nevertheless, our study shows how difficult it is to find them. Apparently the tumor arises within early teratoma, overgrows it quickly and obscures its structure.

The idea of germ cell origin of SCCHT was firmly presented by Ulbright *et al.* [4]. The authors based their view on several pieces of evidence. Firstly, there was the same age range of patients affected by SCCHT and those with malignant germ cell neoplasms (also considered by others). Secondly, they found several histo-, immunohistochemical and ultrastructural features shared by SCCHT and YST, to mention only the intercellular basement membrane-like substance and expression of laminin and  $\alpha$ -1-antitrypsin. And lastly, the authors mentioned an aggressive tumor, similar to SCCHT, that they had observed in a testicular teratoma with seminoma. They concluded that SCCHT is most likely of germ cell origin and might be related to YST [4].

Our finding of YST within the SCCHT population and within teratoma may support this view. As we have presented, tumor cells showed loss of SMARCA4 expression (see further) and the same was observed in YST foci. Nevertheless, YST was not the only structure with negative SMARCA4 staining. Well-differentiated or even benign-looking epithelial elements were also negative for SMARCA4 expression, while immature teratoma displayed diminished reactivity as compared with

normal structures. At least two scenarios are possible with regard to the cell of origin of the SCCHT: it may be a totipotent cell independently giving rise to various teratomatous elements, SCCHT and YST; alternatively some YST cells may undergo partial reprogramming to a somatic lineage. However, we are not aware of any case of SCCHT which developed in clinically manifested YST, which would be expected if the latter hypothesis was valid. YST foci had an immunohistochemical profile distinct from that of SCCHT: they were WT1-negative and strongly positive for pan-cytokeratin, and they might be metastases from the presumed primary focus in the teratoma area.

The finding of a teratomatous component prompted the first author to review germ cell and embryonal tumors of childhood [11, 12]; in effect, a striking similarity of the SCCHT to atypical teratoid/rhabdoid tumor (AT/RT) of the central nervous system (CNS) and malignant renal rhabdoid tumor (MRT) was found. This was further confirmed by analyzing HE slides from several tumors of these types (J.K and W.G., unpublished).

Small cell carcinoma of hypercalcemic type and MRT were first described nearly at the same time. The first group of eleven ovarian tumors published under the name of SCCHT by Dickersin *et al.* came from Scully's consultation series collected in the 1970s [1, 3]. The term “malignant rhabdoid tumor” of kidney was first used in the literature in 1981 by Haas *et al.* [13]. AT/RT has a shorter history – it was first described as MRT of the CNS in 1987 [14].

Apart from many similarities in SCCHT, MRT and AT/RT, small cell carcinoma HT and AT/RT in particular may have foci of epithelial structures and, as is well established for AT/RT and as we have documented, also immature teratomatous elements [12]. Furthermore, germ cell tumors, including teratomas, are common at both sites, with the CNS being at risk, because of presumed mistakes in primitive germ cell migration.

The three tumor types also show striking clinical and molecular similarity. They are polyimmunophenotypic, diploid and genetically stable [6, 15], affect a young population, are highly aggressive and generally show poor responses to chemotherapy. Hypercalcemia is described in both SCCHT and MRT [11, 12, 16], and is attributed to ectopic parathormone expression by the tumors [11, 17, 18]; thus, the difference between them may be rather nosological, although some organ-specific features may be present.

Driven by this similarity we decided to analyze SCCHT for INI-1, and subsequently SMARCA4 expression; INI-1 protein is a core subunit, while SMARCA4 protein is a catalytic ATPase subunit of the SWI/SNF chromatin-remodeling complex [19]. Until recently, loss of INI-1 expression was regarded as a molecular diagnostic feature of MRT and AT/RT [11, 12]. Nevertheless, some AT/RT retain INI-1 expression, and



recently the *SMARCA4* gene was proved to be alternatively inactivated [20]. Loss of *SMARCA4* immunohistochemical staining in both ovarian tumors studied turned out to be due to nonsense alterations in the *SMARCA4* gene, and this is an additional feature shared by our SCCHT with AT/RT. Altogether, our findings place the SCCHT in the same group of tumors as AT/RT and malignant rhabdoid tumor. The latter two are classified as embryonal neoplasms, although indeed their histogenesis is uncertain. Further studies are necessary to decide whether SCCHT, MRT and AT/RT are convergent or overlapping entities.

In summary, we detected foci of immature teratoma in two ovarian SCCHT, found their similarity to malignant rhabdoid tumors, and confirmed their close relationship to that entity by indirectly demonstrating loss of *SMARCA4* function in the SCCHT. Analysis of an additional ten SCCHT is underway and preliminary data appear to support the findings presented. Nevertheless, since we are presenting only two tumors, we are aware of a possibility that the tumors diagnosed as SCCHT may show some heterogeneity.

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The study was approved by the local ethics committee (ref. 13/2008).

*The authors declare no conflict of interests.*

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