Rong Ge¹, Yuqing Chang², Yongli Gan¹, Haidong Zhu³,
Chuangfeng Liu¹

¹Department of Diagnosis, Ningbo Diagnostic Pathology Center, Ningbo, China; ²Department of Pathology, Shibei Hospital, Shanghai, China; ³Department of Radiology, Ningbo Medical Center Lihuili Hospital, Ningbo, China

Contact Dr Yuqing Chang.
E-mail: 18518827@qq.com

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DOI: <https://doi.org/10.1016/j.pathol.2020.04.012>

Gonadoblastoma in individuals with a normal karyotype and no evidence of a disorder of sex development

Sir,

Although the great majority of gonadoblastomas occur in individuals who have dysgenetic gonads associated with disordered sex development and an aberrant karyotype, occasional cases occur in the absence of these findings. Gonadoblastoma occurring in a normal individual is an uncommon, but not a rare, phenomenon. In this article, we examine the clinical and histological findings that distinguish those gonadoblastomas that occur in a normal individual from those that arise in an individual with a disorder of sex development and an abnormal peripheral karyotype. Cases of gonadoblastoma have been reported infrequently in normal women or girls or, exceptionally, in normal men or boys. In a thorough review of the literature, we identified 22 cases that occurred in normal individuals who had no evidence of a disorder of sex development; 15 arose in women, and five occurred in girls less than 18 years of age. The oldest woman was 55 years of age. One case in a 32-year-old woman was originally misdiagnosed as ovarian mixed germ cell-sex cord stromal tumour (MGC-SCST). Only two cases occurred in males, one in a 20-year-old man, and the other in a 9-year-old boy. To summarise, gonadoblastoma occurs occasionally in normal girls or women with 46, XX peripheral karyotype and, exceptionally, in physically normal boys or men with descended testes, no evidence of disordered sex development, and a 46, XY karyotype.

In 1969, De Bacalao and Dominguez¹ reported the first case of gonadoblastoma in a normal individual, and it arose in

a pregnant woman. The following year, Scully² mentioned that case in an addendum to his seminal review on gonadoblastoma, and Salet *et al.*³ reported the first case in a normal girl. In 1990, 20 years later, Elemenoglu *et al.*⁴ reported the next such case of gonadoblastoma in a eukaryotypic woman. In 1976, Arroyo *et al.*⁵ mistakenly reported a case of gonadoblastoma in a normal woman as ovarian MGC-SCST. In 1975, Talerman and Dlemarre⁶ reported the first case of gonadoblastoma in an anatomically normal man, and more than two decades later, Hatano *et al.*⁷ reported the first case in an anatomically normal boy.

All together, we are aware of 22 reported cases of gonadoblastoma in normal individuals. It is now well established that gonadoblastoma occurs occasionally in a normal girl or woman with a 46, XX peripheral karyotype and no evidence of a disorder of sex development.^{8–10} Kim *et al.*¹¹ were the only authors to report more than one case, both in women. One case of gonadoblastoma in a normal individual is unique histologically. The case of Roth *et al.*¹² occurred in a phenotypically normal 9-year-old girl who had a 46, XX peripheral karyotype and a gonadoblastoma associated with a malignant mixed germ cell tumour. Histologically, no germinoma was identified, and anaplastic germ cells were observed in the gonadoblastoma component. The neoplasm likely arose through a molecular pathway that did not involve germinoma.

Table 1 summarises selected aspects of the 22 cases that we found in the literature. Gonadoblastoma in normal individuals occurs considerably more frequently in girls or women with a normal 46, XX peripheral karyotype (91%) than in boys or men with a normal 46, XY karyotype and no evidence of a disorder of sex development (9%). Of the 20 cases that occurred in normal girls or women, 75% occurred in women 18 years of age or older, 10 were fertile, two more were 20 years or older and unmarried, one was 32 years of age with no children, and two were less than 20 years old. Due to its rarity, the incidence of gonadoblastoma in normal individuals within the general population is unknown.

Although no explanation for the occurrence of these neoplasms has been proposed to date, it is likely that they arise through a completely different molecular pathway than those occurring in an individual with disordered sex development. We have no evidence to suggest that the biological behaviour of gonadoblastoma occurring in normal individuals is any different from the those who have an abnormal peripheral karyotype and a disorder of sex development.

Cases in normal individuals have been reported considerably more often in girls or women than in boys or men. Although the histological findings of gonadoblastoma in a normal individual are similar to those who have disordered sex development (Fig. 1), the underlying gonads and the clinical features differ substantially. Unfortunately, some pathologists have mistaken cases of gonadoblastoma in normal girls or women for ovarian MGC-SCST due to a lack of appreciation of this entity.

Further study is required to explain the occurrence of gonadoblastoma in normal individuals. We consider possible explanations that have been proffered in the literature, such as partial gonadal mosaicism or the inability of routine cytogenetics to identify minute or displaced Y chromosomal fragments, to be inadequate because the individuals in our

Table 1 Reported cases of gonadoblastoma in normal individuals

Case no.	Authors and reference	Age, gender, aspects
1	De Bacalao <i>et al.</i> , <i>J Obstet Gynecol</i> 1969; 105:1279–81	28 F fertile
2	Salet <i>et al.</i> , <i>Ann Endocrinol</i> 1970; 31:927–38	16 F female eunuchoidism, amenorrhoea
3	Talerman and Delemarre, <i>J Urol</i> 1975; 113:355–9	20 M
4	Pratt-Thomas and Cooper, <i>Am J Clin Pathol</i> 1976; 65:121–5	22 F fertile
5	Chellam, <i>Indian J Cancer</i> 1981; 18:163–6	25 F fertile
6	Nakashima <i>et al.</i> , <i>Hum Pathol</i> 1989; 20:814–16	28 F fertile
7	Elemenoglou <i>et al.</i> , <i>Arch Geschwulstforsch</i> 1990; 60:223–6	28 F fertile
8	Erhan <i>et al.</i> , <i>J Clin Pathol</i> 1992; 45:525–9	26 F pregnant
9	Obata <i>et al.</i> , <i>Gynecol Oncol</i> 1995; 58:124–8	10 F
10	Arroyo <i>et al.</i> , <i>Int J Gynecol Pathol</i> 1998; 17:281–3	32 F originally misdiagnosed, no pregnancies
11	Hatano <i>et al.</i> , <i>Int J Urol</i> 1999; 6:164–6	9 M
12	Zhao <i>et al.</i> , <i>Pathol Int</i> 2000; 50:332–5	27 F fertile
13	Kim <i>et al.</i> , <i>Korean J Pathol</i> 2003; 37:66–70 Case 1	33 F unmarried
14	Kim <i>et al.</i> , <i>Korean J Pathol</i> 2003; 37:66–70 Case 2	30 F fertile
15	Cooper <i>et al.</i> , <i>Pathology</i> 2007; 39:284–5	55 F fertile
16	Gelincik <i>et al.</i> , <i>Indian J Pathol Microbiol</i> 2010; 53:345–6	18 F no mention of marital status
17	Yilmaz <i>et al.</i> , <i>J Obstet Gynaecol Res</i> 2010; 36:697–700	20 F unmarried
18	Esin <i>et al.</i> , <i>Arch Gynecol Obst</i> 2012; 285:447–51	15 F
19	Kanagal <i>et al.</i> , <i>J Clin Diag Res</i> 2013; 7:2021–2	14 F
20	Gru <i>et al.</i> , <i>Am J Surg Pathol</i> 2017; 41:1290–7	24 F fertile
21	Arafah and Raddaoui, <i>Int J Surg Pathol</i> 2018; 26:287–92	19 F
22	Roth <i>et al.</i> , <i>Int J Gynecol Pathol</i> 2019; 38:581–7	9 F

F, female; M, male.

Fig. 1 Gonadoblastoma in a woman with a normal peripheral karyotype and no evidence of a disorder of sex development. (A) Mature follicles within cellular ovarian stroma are superficial to classical gonadoblastoma with extensive calcification. (B) Area of classical gonadoblastoma consists of closely packed rounded islands comprised of a mixture of germ cells, sex cord elements, and hyaline bodies. (C) Note the two types of germ cells, both with abundant clear cytoplasm. (D) The benign appearing germ cells have small compact nuclei, and the premalignant ones have enlarged vesicular nuclei with clumped chromatin and frequent mitotic figures. (E) Note the trabecular pattern of the 'dissecting' variant. (F) Rounded hyaline bodies are prominent in the 'dissecting' variant, and hyaline material is observed between the trabeculae.

study were both physically and genetically normal in all reported cases; furthermore, two-thirds of the women in our study were fertile.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

Lawrence M. Roth¹, Bernard Czernobilsky², Mahmut Akgul¹, Liang Cheng^{1,3}

¹Department of Pathology, Indiana University School of Medicine, Indianapolis, IN, USA; ²Patho-Lab Diagnostics Ltd, Ness Ziona, Israel; ³Department of Urology, Indiana University School of Medicine, Indianapolis, IN, USA

Contact Lawrence M. Roth, MD.

E-mail: lroth@iupui.edu

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DOI: <https://doi.org/10.1016/j.pathol.2020.04.011>

Hybrid sclerosing epithelioid fibrosarcoma/low grade fibromyxoid sarcoma arising in the small intestine with distinct *HEY1-NCOA2* gene fusion

Sir,

Sclerosing epithelioid fibrosarcoma (SEF) and low grade fibromyxoid sarcoma (LGFMS) are malignant fibroblastic neoplasms that are believed to be related and belong to the same lesional spectrum.^{1–3} Some cases morphologically show features of both SEF and LGFMS and they are known as hybrid SEF/LGFMS.^{2–5} There are similarities between both entities at morphological, immunohistochemical and molecular levels.^{1,3} LGFMS is relatively more common than SEF and has a less aggressive clinical course in the first 5 years following excision in terms of local recurrence and distant metastasis.^{1,2,4} The majority of LGFMS cases exhibit t(7;16) chromosomal translocation resulting in *FUS-CREB3L2* gene fusion, and a lower percentage of cases can display t(11;16) with *FUS-CREB3L1* fusion.^{1–4} However, *EWSR1-CREB3L1* gene fusion has shown to be a recurrent alteration in SEF.^{2–4} Herein, we report an unusual case of intra-abdominal hybrid SEF/LGFMS harbouring *HEY1-NCOA2* gene fusion, an alteration that has not been previously described to occur in SEF, hybrid SEF/LGFMS or LGFMS.

A 48-year-old male patient presented with acute abdominal pain and was diagnosed to have intestinal obstruction caused by a small bowel mass. A laparotomy was then performed with partial resection of the small intestine including the mass. Histopathology showed an infiltrative cellular tumour

arising from the small bowel wall, predominantly composed of epithelioid cells arranged in cords and nests in a densely sclerotic hyalinised stroma, while in other areas the tumour had variable cellularity with hypocellular and hypercellular areas of spindle cells in fibromyxoid stroma (Fig. 1A–C). By immunoperoxidase stains, the tumour cells showed patchy staining for EMA and strong diffuse reactivity for MUC4 (Fig. 2A,B). However, there was negative staining for cytokeratin AE1/AE3, DOG1, CD117, CD34, S100, smooth muscle actin (SMA) and desmin. The diagnosis of malignant epithelioid and spindle cell neoplasm consistent with hybrid SEF/LGFMS was rendered. Imaging studies showed multiple liver and bone lesions in the pelvis, sternum and the 8th thoracic vertebra, consistent with metastasis. The patient sought treatment at our institution, and he received 10 fractions of radiotherapy for the bone metastasis and three cycles of chemotherapy (cyclophosphamide and adriamycin). A month later, positron emission tomography/computed tomography (PET/CT) scan showed partial response, so he received another seven cycles of chemotherapy then started on pazopanib. PET/CT scan showed partial response in the bone metastasis. Magnetic resonance imaging (MRI) of the liver showed multiple hepatic focal lesions scattered in both lobes. Ultrasound-guided liver core biopsy revealed infiltration of the tumour showing SEF-like areas with absence of LGFMS component (Fig. 1D). Molecular analysis using Human Methylation 850 (850k) Array (Illumina, USA) on tumour DNA extracted from formalin fixed, paraffin embedded (FFPE) tissue detected segmental losses on chromosome 9, loss of chromosome 11p and 22 (including homozygous loss of SMARCB1). RNA sequencing via next-generation sequencing (TruSeq RNA Access, NextSeq; Illumina) on RNA extracted from FFPE tissue was then performed to find an actionable gene mutation so the patient could benefit from targeted therapy. Interestingly, *HEY1-NCOA2* gene fusion was detected (Fig. 3). Following that, the patient travelled back to his home country, and clinical follow-up was eventually lost.

SEF and LGFMS are malignant fibroblastic neoplasms that are closely related at the morphological, immunohistochemical and molecular levels.^{1,3} Morphologically, SEF is composed of epithelioid tumour cells forming cords and nests in a dense hyalinised sclerotic stroma. LGFMS is characterised by having hypocellular and hypercellular areas of spindle cells in fibromyxoid stroma. Both entities are usually positive for MUC4 immunostain. SEF is a more aggressive tumour with high risk of recurrence and distant metastasis.^{2–4} LGFMS has less aggressive behaviour with much lower risk for recurrence and metastasis than SEF in the first 5 years following excision; however, metastasis can occur at high rates later on long-term follow-up.^{1,2,4} Some tumours display morphological features of both SEF and LGFMS and they are known as hybrid SEF/LGFMS.^{2–4}

SEF arises most commonly in the lower extremities followed by upper extremities and trunk. Rarely, it can develop in the bone and viscera with few cases reported to occur in the intestine, pancreas, liver and kidney.^{6–10} Those cases that arise from the deep viscera can grow significantly before they are detected, so they may behave more aggressively. The tumour in our case was arising from the wall of the small intestine. The tumour had an aggressive clinical course with bone and hepatic distant metastasis.