To date, there are no validated treatment guidelines due to limited data, but the best approach documented for localised disease is a wide local excision or mastectomy with negative resection margins. Removal of axillary lymph node is optional. Crèvecoeur *et al.* reported their patient developed an osteosarcoma in the other breast, 15 months after the discovery of the first tumour, and no axillary lymphadenopathy was observed.⁷ These tumors have a propensity for blood-borne rather than lymphatic spread. Among skeletal osteosarcoma, TOS is exquisitely sensitive to modern chemotherapy but there is no literature about mammary TOS treated with chemotherapy.⁸ The benefits of chemotherapy administration should be weighed against the side effects, especially in older or unfit patients. Indications for radiation therapy, in the absence of specific data on breast sarcoma, probably could follow those for soft-tissue sarcomas in general. We suggested that our patient undergo chemotherapy, however the patient refused further treatment on consideration.

Prognostic factors of primary breast osteosarcoma include tumour size, number of mitoses, presence of stromal atypia, histological subtype and resection margin involvement. Among them, size of the tumour tends to be the most important factor affecting prognosis. A better survival rate for patients with smaller (<4.6 cm) tumours has been observed. The most common sites of metastases include the lung, bone, brain, subcutaneous tissue and heart.⁴ Our patient is presently disease free close to 3.0 years following surgery. The good prognosis is probably associated with small tumour size (<4.6 cm), early diagnosis, no metastasis and clean margin by mastectomy. However, primary breast osteosarcomas are considered highly aggressive tumours associated with early recurrence. Lack of follow-up and late recurrence/metastases are common in osteosarcomas, so our patient still requires close follow-up.

Breast TOS is a very uncommon malignancy where a definitive diagnosis is established on the basis of the typical histological architecture and cellular morphology, coupled with immunohistochemical profile. Surgical excision with clear margins remains the cornerstone of treatment and lymph node dissection could be optional. Further studies are required to clarify the biological behaviour of such tumours and optimise therapeutic strategies. Our case represents a very unusual variant of primary breast osteosarcoma and the first of its kind reported in the literature.

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1. Yin JQ, Fu YW, Xie XB, *et al.* Telangiectatic osteosarcoma: outcome analyses and a diagnostic model for differentiation from aneurysmal bone cyst. *J Bone Oncol* 2017; 11: 10–6.
2. Graadt van Roggen JF, Zonderland HM, Welvaart K, *et al.* Local recurrence of a phyllodes tumor of the breast presenting with widespread differentiation to a telangiectatic osteosarcoma. *J Clin Pathol* 1998; 51: 706–8.
3. Matsumoto H, Nakachi S, Kosuge N, *et al.* Metaplastic carcinoma of the breast with widespread telangiectatic form of osteosarcomatous differentiation. *Pathol Int* 2016; 66: 236–8.
4. Silver S, Tavassoli FA. Primary osteogenic sarcoma of the breast: a clinicopathologic analysis of 50 cases. *Am J Surg Pathol* 1998; 22: 925–33.
5. Gao Z-H, Yin J-Q, Liu D-W, *et al.* Preoperative easily misdiagnosed telangiectatic osteosarcoma: clinical-radiologic-pathologic correlations. *Cancer Imaging* 2013; 13: 520–6.
6. Song W, Suurmeijer AJH, Bollen SM, *et al.* Soft tissue aneurysmal bone cyst: six new cases with imaging details, molecular pathology, and review of the literature. *Skeletal Radiol* 2019; 48: 1059–67.
7. Crèvecoeur J, Jossa V, Gennigens C, Parmentier JC, Crèvecoeur A. Primary osteosarcoma of the breast: a case report. *Clin Case Rep* 2015; 4: 62–6.
8. Kurata K, Anan K, Ishikawa N, *et al.* A case of primary extraskeletal osteosarcoma of the breast. *Surg Case Rep* 2018; 4: 121.

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Histiocytic sarcoma arising from thyroid gland with *BRAF* V600E mutation

Sir,

Histiocytic sarcoma (HS) is a relatively rare tumour composed of malignant cells showing morphological and immunophenotypic characteristics of mature histiocytes,¹ accounting for less than 1% of all malignancies of the haematopoietic system. In this report, we illustrate this rare tumour with its unique location and the presence of the *BRAF* V600E mutation.

A 71-year-old woman presented with a 1-year history of gradually enlarging neck mass. The patient complained of difficulty in swallowing for a month. Physical examination showed a painless mass in the left cervical region and no systemic lymph node enlargements. Laboratory studies revealed TSH was 9.068 mIU/L (normal range 0.350–4.940 mIU/L). Thyroid ultrasound showed a 4.2×3.9×3.0 cm nodule in the left lobe and chest computed tomography revealed a locally advanced thyroid mass producing significant deviation of the trachea (Fig. 1A). No metastases were detected by magnetic resonance imaging (MRI). Aspiration cytology suggested the possibility of a medullary thyroid carcinoma. The patient underwent total thyroidectomy. The patient refused further treatment, and died of pulmonary failure caused by bronchopneumonia at 3 months after the operation.

Grossly, the left lobe of the thyroid measured 5×4×4 cm and the right lobe was 3×2×2 cm. The cut surface of the left lobe revealed a well-circumscribed but unencapsulated tumour measuring 3 cm in diameter, which was golden coloured and soft in consistency (Fig. 1B). The right lobe was unremarkable. Microscopically, tumour cells showed diffuse, scattered or sheet-like growth in the left lobe of the thyroid. They were monomorphic to pleomorphic in shape. The

Fig. 1 (A) Computed tomography shows a mass in the left lobe of thyroid. The trachea is shifted to the right. (B) Gross picture of the tumour.

Fig. 2 (A) Haematoxylin and eosin staining of the tumour. (B) Tumour cells are positive for CD163.

cytoplasm was abundant and pale to eosinophilic with indistinct cytoplasmic membranes (Fig. 2A). Nuclei were round, oval or irregular with prominent nucleoli. Mitotic figures were prominent in some areas. Phagocytosis was seen in part of some tumour cells. Bizarre multinuclear giant cells were dispersed among them. Some lymphocytes and plasma cells surrounded the tumour.

Immunohistochemically, tumour cells were diffusely positive for CD163 (Fig. 2B), CD68 (both KP-1 and PG-M1), vimentin and CD4, almost half were positive for lysozymes, and focally (20%) positive for CD31. Tumour cells revealed no staining for AE1/AE3, CAM52, CK19, CK5/6, P63, PAX-5, PAX-8, CD1a, langerin, CD79a, CD45RO, CD21, CD34, CD30, EMA, ALK, lymphocyte common antigen (LCA), myeloperoxidase, S-100 protein, ETS-related gene (ERG), F8, thyroid transcription factor, synaptophysin, chromogranin A, calcitonin, thyroid globulin, parathyroid hormone and HMB-45. The labelling index of Ki-67 (MIB-1) was 70%. *In situ* hybridisation analysis for EBER showed no apparent positive signal in the tumour cells. *IgH* rearrangement was not observed on polymerase chain reaction (PCR). These biopsy findings led us to a diagnosis of HS. The tumour revealed a *BRAF* V600E mutation by amplification refractory mutation system (ARMS)-PCR.

HS is a malignancy of haematopoietic origin composed of cells displaying morphological and immunophenotypic features of histiocytic differentiation.¹ Bona fide cases of HS are exceptionally rare in the world literature, and series reports are limited in number. HS mainly involve lymph nodes, the skin, and the gastrointestinal tract. HS of the thyroid gland is

extremely rare and only three cases of the entity have been reported thus far.^{2–4} The diagnosis of HS is usually challenging and mainly based on histological and immunohistochemical criteria.

The differential diagnosis of thyroid HS includes undifferentiated carcinoma, Langerhans cell histiocytosis, the vastly more common large cell non-Hodgkin lymphomas (DLBCL and ALCL), and metastatic melanoma. Undifferentiated carcinoma of thyroid in origin, metastatic carcinoma, and melanoma can be excluded with negative AE1/AE3, CAM5.2, CK19, EMA, TTF-1, thyroid globulin, HMB-45 and Melan-A expression. Langerhans cell histiocytosis and dendritic cell tumours can be ruled out by the absence of langerin, CD1a, CD21 and CD35. The lack of CD20, CD79a, PAX-5, CD3, ALK and CD30 expression excludes DLBCL and ALCL.

Patients with HS usually present at an advanced stage and have poor prognosis. Recently, a small number of case reports have demonstrated the presence of the *BRAF* mutation in HS.^{5,6} We report the first case of HS harbouring *BRAF* V600E mutation in thyroid gland. Molecular therapy targeting the *BRAF* mutation has been applied in clinical practice for several cancer types. Although the frequency in HS is uncertain, it is necessary to investigate *BRAF* V600E mutation as a potential therapeutic target in the future.

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1. Swerdlow SH, Campo E, Pileri SA, *et al.* The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016; 127: 2375–90.
2. Yu L, Yang SJ. A case of primary histiocytic sarcoma arising from thyroid gland. *Pathol Oncol Res* 2010; 16: 127–32.
3. De Vos FY, Gerding MN, Arends JW, *et al.* Histiocytic sarcoma localized in the thyroid: a case report. *Ann Hematol* 2008; 87: 681–2.
4. Munoz J, Sanchez BE, Wang D. Histiocytic sarcoma of the thyroid. *Am J Hematol* 2012; 87: 531.
5. Michonneau D, Kaltenbach S, Derriex C, *et al.* BRAF(V600E) mutation in a histiocytic sarcoma arising from hairy cell leukemia. *J Clin Oncol* 2014; 32: e117–21.
6. Vaughn JL, Freitag CE, Hemminger JA, *et al.* BRAF V600E expression in histiocytic sarcoma associated with splenic marginal zone lymphoma: a case report. *J Med Case Rep* 2017; 11: 92.

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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