was misjudged as a sole pyogenic granuloma. In contrast to our case, the component of the pyogenic granuloma was probably not visible due to the subjacent naevus. Angiogenic factors emanating from the epithelial and the naevus component may have led to the development of the pyogenic granuloma.

Studies on angiogenic factors, in particular vascular endothelial growth factor (VEGF) in melanocytic tumours of the skin, are contradictory. Pisacane *et al.* found an increase of VEGF in most naevi using immunohistochemistry⁴ while Einspahr *et al.* found almost no VEGF expression in benign naevi but elevated expression in dysplastic naevi and melanoma.⁵ Our case was diagnosed as a completely benign naevus and would be more consistent with the results of Pisacane's study.

In summary, a pyogenic granuloma developing on a naevus might simulate progression of a conjunctival naevus into a melanoma.

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Unique and distinctive histological features of immunotherapy-related thyroiditis

Sir,

Immune check-point inhibitor (ICI) therapy is now considered part of the standard of care in oncology for a range of malignancies including melanoma, lung cancer, head and neck cancers and kidney cancer.¹ In the normal physiological setting, programmed cell death protein 1 (PD-1) is expressed when immune cells are activated, and functions to maintain self-tolerance when it binds to programmed death-ligand 1 (PD-L1) on haematopoietic and non-haematopoietic cells.^{1–4} In many malignancies, PD-L1 is overexpressed on cancer cells, allowing them to evade attack by the immune system.⁴

Anti-PD-1 or PD-L1 are a specific class of immunotherapy that prevent this immune evasion via the PD-1/PD-L1 pathway and thereby enhance the body's own immune response to attack cancer cells.

Unfortunately, alteration of immune tolerance with ICI can result in autoimmune-like inflammatory side effects in a range of organs. Immunotherapy-related thyroiditis is one of the most common and well recognised side effects.⁵ Of note, this thyroiditis is usually diagnosed biochemically and treated conservatively. Therefore, the morphological features of this clinically distinct type of thyroiditis are not well described or recognised. Here we report the surgical pathology of this distinctive pattern of thyroiditis in a patient who underwent diagnostic hemithyroidectomy during treatment with nivolumab, a PD-1 inhibitor.

A 55-year-old male was diagnosed with stage III melanoma. A staging fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan revealed a hot nodule in the left lobe of the thyroid with an SUV of 4.3. The nodule was palpable and thyroid ultrasound confirmed a 10 mm lesion in the left mid-thyroid with punctate microcalcification, a mixed solid and cystic appearance and some internal vascularity. It was assigned a TI-RADS category of 4 (moderately suspicious). A fine needle aspiration (FNA) was subsequently performed and classified as Bethesda category 4 (suspicious for follicular neoplasm). The patient was then commenced on nivolumab. He was otherwise well with no other significant medical or surgical history and no clinical features or past history of thyroid disease.

Blood tests performed 4 weeks after commencement of nivolumab indicated asymptomatic thyrotoxicosis with an undetectable thyroid-stimulating hormone (TSH) of 0 (0.40–4.00 mIU/L), free T4 of 28.4 (9.0–19.0 pmol/L) and free T3 of 12.4 (2.6–6.0 pmol/L) and a diagnosis of subclinical immunotherapy related thyroiditis was made. Anti-thyroid antibodies were not performed. A decision was made to proceed to a diagnostic left hemithyroidectomy to assess the Bethesda category 4/TI-RADS category 4 thyroid nodule. Surgery was uncomplicated and material was submitted for pathological examination.

On gross examination, the excised left lobe of thyroid weighed 11 g, and was diffusely firm and pale. The cut surface had a micronodular appearance that resembled Hashimoto's thyroiditis and the suspicious nodule was now 4 mm in diameter. Microscopic examination showed a very unusual and distinctive pattern of thyroiditis. There was widespread infiltration by lymphocytes, generally as individual cells rather than clusters or lymphoid follicles, often closely associated with the follicular epithelium (Fig. 1). There was subtle atrophy which enhanced the underlying lobular architecture of the thyroid. Most of the follicles showed colloid depletion. The follicles were lined by enlarged follicular cells without Hürthle cell change and showed prominent infiltration of the follicular epithelium by lymphocytes, resembling lymphoepithelial-like lesions (Fig. 1B). The 4 mm nodule comprised mildly dilated follicles with similar intraepithelial lymphocytosis within background sclerotic stroma, suggestive of a pre-existing adenomatoid nodule that had regressed after treatment. There were no nuclear features of papillary thyroid carcinoma.

Immunohistochemistry demonstrated that the majority of lymphocytes were T-cells with only occasional aggregates of

Fig. 1 Immunotherapy-induced thyroiditis. (A) Thyroid shows prominent lobulation attributable to early atrophy (H&E). (B) The follicles show colloid depletion and dense infiltration by individual T-lymphocytes resembling lymphoepithelial lesions (H&E). (C) CD20 (B-cell marker) immunohistochemistry highlights only scattered aggregates of B-cells in the stroma surrounding the lobules. (D) CD3 (T-cell marker) immunohistochemistry demonstrates that the lymphocytes infiltrating and damaging the follicles are predominantly T-cells.

CD20+ B-cells being found in the stroma between the lobules (Fig. 1C). The overwhelming majority of lymphocytes were CD3+ T-cells and these were found predominantly within the lobules where many were closely opposed to the follicular epithelium suggesting T-cell mediated immune damage (Fig. 1D). Further immunohistochemistry (Fig. 2) demonstrated that the T-cells were predominantly CD8+ with a CD4:CD8 ratio of 1:4. PD-1 was overexpressed in the

T-cells (Fig. 2C) and PD-L1 showed overexpression in follicular cells (Fig. 2D).

For comparison, we stained one normal thyroid, which showed no expression of PD-L1 in follicular cells, and one case of Hashimoto thyroiditis, which showed induced expression with PD-L1. Of note, this case differed from Hashimoto thyroiditis morphologically due to its peculiar pattern of T-cell mediated follicle damage as well as the

Fig. 2 Immunohistochemistry of immunotherapy-induced thyroiditis. (A) Few of the T-cells infiltrating the follicles are CD4+, (B) with the overwhelming majority being CD8+. (C) PD-1 immunohistochemistry shows increased expression predominantly in inflammatory cells. (D) PD-L1 immunohistochemistry shows increased expression predominantly in thyroid follicular cells.

absence of lymphoid follicles, and absence of Hürthle cell change.

A pathological diagnosis of immunotherapy-related thyroiditis with a partially regressed adenomatoid nodule was made. Recovery was uneventful and follow up thyroid function tests 4 weeks after surgery revealed mild hypothyroidism with a TSH of 9.22 (0.40–4.00 mIU/L), free T4 of 7.3 (9.0–19.0 pmol/L) and free T3 of 2.2 (2.6–6.0 pmol/L), further supporting the diagnosis of immunotherapy-induced thyroiditis.

Thyroid dysfunction is one of the most common side effects associated with ICIs. The reported rate of thyroid dysfunction due to PD-1 inhibitors is as high as 21% in patients taking pembrolizumab and 29% in patients taking nivolumab.^{6–8} Thyroid dysfunction typically manifests as either hypothyroidism, or more commonly transient thyrotoxicosis followed by hypothyroidism soon after treatment, as in our case.^{6–9} Studies with long-term follow-up suggest there is usually no resolution of hypothyroidism once it has developed.⁹

As immunotherapy-related thyroiditis is usually managed medically, the histological correlates of this condition are not well described and rarely recognised by surgical pathologists. The most striking feature in this case was widespread infiltration of the thyroid follicles by CD8+ T-cells, in many areas resembling the lymphoepithelial lesions more characteristic of (B-cells in) MALT lymphoma. This T-cell mediated follicular damage was associated with colloid depletion and atrophy leading to an exaggeration of the underlying lobular architecture of the thyroid.

These morphological features are quite different to those seen in other forms of thyroiditis including Graves' disease, characterised by diffuse hyperplasia rather than atrophy, and Hashimoto thyroiditis, characterised by heavy (predominantly B-cell) lymphocytic infiltration often as sheets of lymphocytes rather than individual T-cell damaging follicles. To our knowledge the surgical pathology of only two previous cases of immunotherapy related thyroiditis have been reported.^{8,10} In one case, induced by pembrolizumab, the morphological features were very similar, including a firm nodular thyroid with a T-cell dominant immune response associated with destruction of the follicles.⁸ Another case,¹⁰ occurring secondary to nivolumab, also showed a slightly enlarged firm gland with increased lobulation and lymphocyte-mediated follicle damage but with the addition of non-necrotising granulomas which were absent in our case.

We conclude that the histology of immunotherapy-induced thyroiditis, although rarely described, is distinctive and characterised by CD8+ T-cell mediated destruction of follicles with secondary colloid depletion. This leads to secondary atrophy which exaggerates the underlying lobular architecture of the thyroid and gives the impression of a firm nodular gland. With awareness, these features can be readily recognised in clinical practice based on morphology alone with routine haematoxylin and eosin stained sections.

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A rare case of metastatic lung carcinoma with t(15;19)(q13;p13.1) and trisomy 12

Sir,

Carcinoma with translocation t(15;19)(q13;p13.1) is a rare lethal human cancer which occurs more frequently in young people.^{1,2} It was first reported by Kubonishi *et al.* in 1991 in a young adult with aggressive thymic carcinoma.³ This carcinoma is also known as nuclear protein in testis (NUT) midline carcinoma due to its characteristic chromosomal translocation involving NUT, a novel gene on chromosome 15q13 and its unique involvement of midline structures such as the sinus/orbit, nasopharynx, trachea, thymus, mediastinum, lungs and bladder.^{2,4} Unlike most cases of aggressive carcinoma which have complex karyotypes and lack diagnostic balanced translocation, the cytogenetic profile of NUT