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Case Report

CASE REPORT

Poorly differentiated adenocarcinoma of an unknown primary with a thyroid tumour and an aggressive course: thyroid or lung carcinoma?

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Abstract

Cancers of unknown primary (CUPs) are challenging for physicians to diagnose and treat. Metastases to the thyroid gland are rare, representing less than 1% of all thyroid malignancies. Here, we report a case of a 69-year-old Asian man who had both thyroid gland and lymph node enlargement in the neck and shoulders but no nodules/tumours in the lung field. The patient died 51 days after his first visit to our office, although pembrolizumab was administered on day 34 based on programmed cell death-ligand 1 (PD-L1) expression. Immunohistochemistry (IHC) with paired box 8 (PAX8) may be useful to diagnostically distinguish poorly differentiated lung adenocarcinomas from napsin A-positive thyroid carcinomas.

INTRODUCTION

Cancers of unknown primary (CUPs) are metastatic tumours whose primary site cannot be identified during pretreatment evaluation [1]. Adenocarcinomas of unknown primary account for approximately 70% of CUPs [2]. The median survival of patients with adenocarcinomas is 3 months, with a 17% 1-year survival rate [3].

When tumour(s) are identified within the thyroid gland, metastases to the thyroid gland or secondary involvement by direct extension from a nonthyroid malignancy in the neck must be considered. However, metastases to the thyroid gland represent less than 1% of all thyroid malignancies [4, 5]. Common primary sites for thyroid metastases include the kidneys, head, neck (squamous cell carcinomas), lung and breast [4, 5].

Here, we report a case of a patient who complained of neck stiffness at his first visit to our office and died after an aggressive disease course. A computed tomography (CT) scan showed no nodules/tumours in the lung field but thyroid gland and lymph node enlargement in the neck and shoulders. Fine needle aspiration (FNA) biopsies from the thyroid tumour and from a subcutaneous tumour in the left shoulder revealed a poorly differentiated adenocarcinoma of unknown primary. Immunohistochemistry (IHC) suggested that the tumour was likely a poorly differentiated lung adenocarcinoma.

CASE REPORT

A 69-year-old Asian man was referred to our office for neck stiffness and persistent coughing for over a month. His past medical history was significant for gastric and duodenal ulcers that improved after *H. pylori* eradication. He had smoked 15 cigarettes per day for 50 years. His physical examination

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revealed subcutaneous, board-like indurations and nodules/tumours without bilateral supraclavicular and cervical tenderness.

Contrast-enhanced CT scanning revealed enlargement of the thyroid gland (i.e. a thyroid tumour), which displaced the trachea to the left side and subcutaneous nodules/tumours that displaced the sternocleidomastoid muscle anteriorly (Fig. 1). High-resolution CT scanning revealed no nodules/tumours in the lung field as shown in Video 1 of the supplementary material. To clarify the cytopathological features of the subcutaneous nodules/tumours, the patient was referred to our otolaryngologist, who performed fine needle aspiration (FNA) biopsies on the subcutaneous tumour in the left supraclavicular region as well as on the thyroid tumour (Fig. 1).

Nine days after his first visit to our office, the patient was transferred to our emergency department by ambulance due to severe chest tightness. Cardiac echography and a plain CT scan showed cardiac tamponade (data not shown; Fig. 2); therefore, continuous pericardial drainage was performed.

Cytological analysis of the FNA biopsies of the subcutaneous and thyroid tumours as well as of the pericardial effusion, indicated a CUP, possibly an undifferentiated adenocarcinoma (data not shown).

On day 12, an excisional biopsy was performed for extensive IHC analyses on the subcutaneous tumours in the left supraclavicular region (Figs 3 and 4). Table 1 summarizes the IHC results for pan-keratin antibodies AE1 and AE3 (AE1/3), cytokeratin 7 (CK7), cytokeratin 20 (CK20), thyroid transcription factor-1 (TTF-1), napsin A, vimentin, calretinin, p40, paired box 8 (PAX8), and carcinoembryonic antigen (CEA). (PAX8 staining was performed after the patient was deceased.) The patient's serum CEA levels were 13.4 ng/ml (day 1), 520.5 ng/ml (day 10) and 596.6 ng/ml (day 50).

Finally, on day 34, pembrolizumab was administered at 200 mg/kg body weight, starting day 1, q3w based on the strong intensity and 100% positivity of the tumour cells with programmed cell death-ligand 1 (PD-L1) staining with anti PD-L1 antibody 22C3, however, the patient died on day 51.

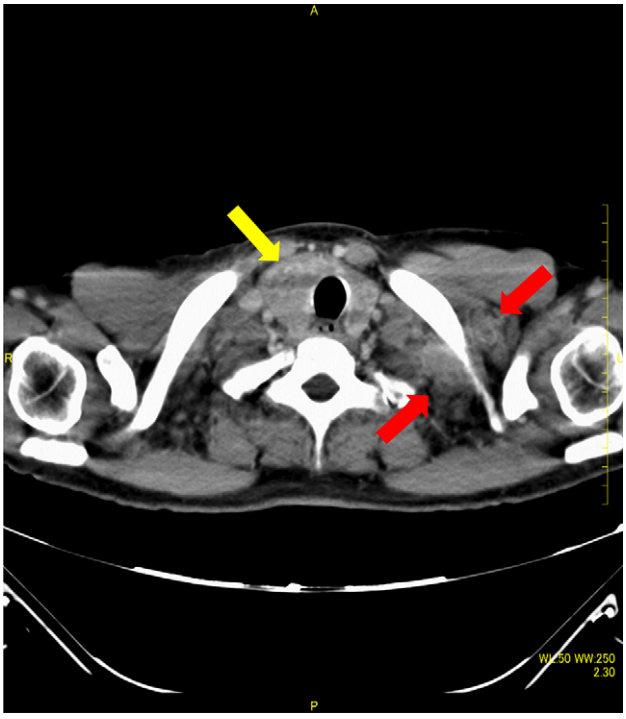

Figure 1: Contrast-enhanced CT scan showing the thyroid tumour (yellow arrow) and subcutaneous nodules/tumours in the left supraclavicular region (red arrows). The thyroid gland and lymph nodes were enlarged in the neck and shoulders.

DISCUSSION

The primary cancer site in the patient report here clinically appeared to be the thyroid gland (i.e. a poorly differentiated thyroid carcinoma) because 1) the major lesions were on both sides of the cervical to supraclavicular areas and included thyroid gland enlargement (Fig. 1); 2) FNA biopsy of the thyroid tumour revealed a poorly differentiated carcinoma with the same pathology as the subcutaneous tumour in the left supraclavicular region; and 3) no tumours/nodules were found in the lung field (Video 1 of the supplementary material).

Conversely, IHC suggested that the lung was the primary cancer site in the patient; however, the difficulties that the patient experienced and the aggressive course of the disease made reaching a diagnosis challenging. TTF-1 and napsin A positivity are reported to reliably enable distinguishing primary from metastatic tumours of the lung [6, 7]. Napsin A expression was less intense and partially positive in the patient, while TTF-1 was positive (Fig. 4). Napsin A has a higher specificity of 96% but a lower sensitivity of 65% for metastatic lung adenocarcinoma compared with TTF-1 expression (81% for each measure) [6]. Furthermore, poorly differentiated thyroid carcinomas may be napsin A-positive [8]. TTF-1 is also positive in thyroid tumours, regardless of histologic type, and in lung carcinomas, including 75% of adenocarcinomas [7]. Therefore, PAX8 may have a crucial role in diagnostically distinguishing napsin A-positive thyroid carcinomas from lung adenocarcinomas, which are PAX8 negative, as in our patient [7, 8]. PAX8 stain positivity is also diagnostically useful for müllerian, renal, and thymic carcinomas and pancreatic endocrine tumours [7]. Further, thyroglobulin staining might be useful for distinguishing

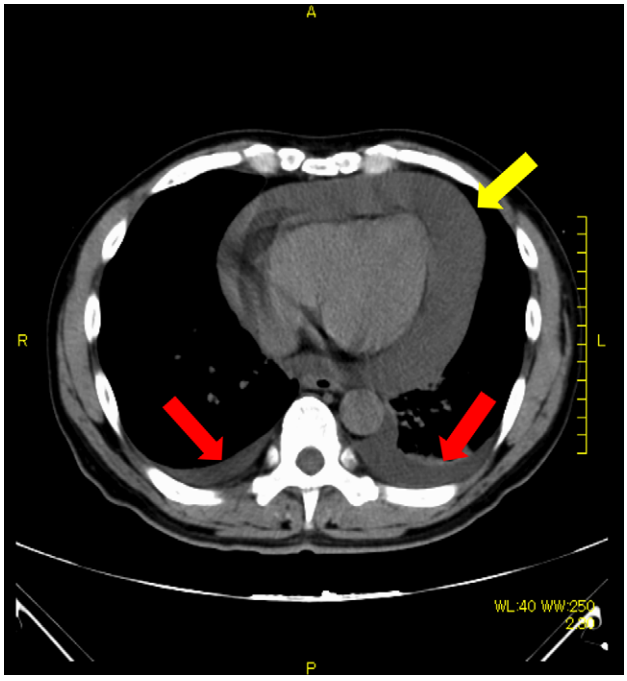

Figure 2: Plain CT scan showing the cardiac tamponade caused by pericardial effusion (yellow arrow) and pleural effusion (red arrows). The pericardial effusion displaced the cardiac muscle.

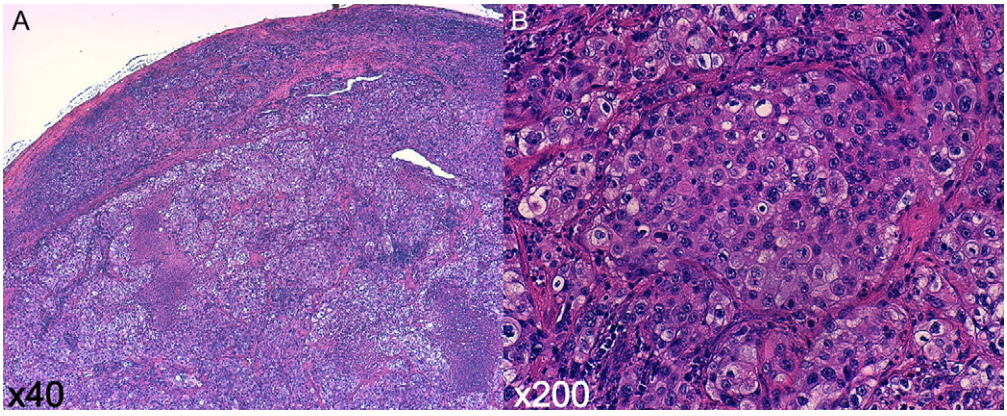

Figure 3: Haematoxylin and eosin (HE) staining of a subcutaneous tumour in the left supraclavicular region. (**A**) Low magnification (×20); (**B**) High magnification (×200). Proliferation of atypical cells with enlarged nuclei and nucleoli with solid and alveolar configurations without keratinization or ductal formation.

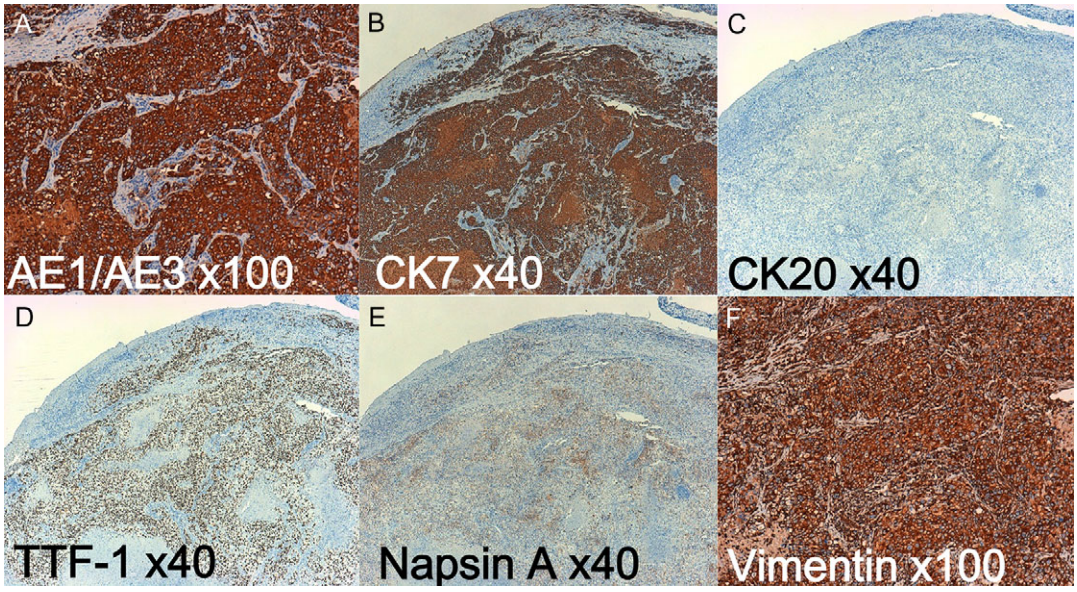

Figure 4: IHC staining of a subcutaneous tumour in the left supraclavicular region. (**A**) AE1/3 (×100); (**B**) CK7 (×40); (**C**) CK20 (×40); (**D**) TTF-1 (×100); (**E**) Napsin A (×40); (**F**) Vimentin (×100). Pan-keratin AE1/3-positive, CK7-positive, CK20-negative, and TTF-1-positive tumours suggested thyroid or lung carcinomas. As shown in Table 1, vimentin expression is uncommon in lung adenocarcinomas but may be positive in undifferentiated metastatic lung adenocarcinomas.

Table 1: Summary of IHC in poorly differentiated thyroid carcinoma and lung adenocarcinoma [7]

	AE1/3	CK7	CK20	TTF-1	napsin A	vimentin	calretinin	p40	PAX8	CEA
Patient	+	+	–	+	partly +	+	–	–	–	+*
Thyroid	+	+	–	+	partly +**	+	–	–	+	–
Lung	+	+	–	+	+	partly +***	–	–	–	+

AE1/3: pan-keratin antibodies AE1 and AE3; CK7: cytokeratin 7; CK20: cytokeratin 20; TTF-1: thyroid transcription factor-1; PAX8: paired box 8; CEA: carcinoembryonic antigen.
Please note that the percentage expression of each stain may vary among samples from each carcinoma [7].
*Serum CEA levels in the patient were elevated, as shown in the text.
**Napsin A expression is uncommon but could be positive in poorly differentiated thyroid carcinomas [7, 8].
***Vimentin expression is uncommon but could be positive in undifferentiated or metastatic lung adenocarcinomas [7, 10].

thyroid from lung primaries if differentiation to mature thyroid glands is partially preserved [7].

Pembrolizumab was reported to result in significantly longer progression-free and overall survival than platinum-based chemotherapy in patients with advanced non-small cell lung cancer and PD-L1 expression on at least 50% of tumour cells [9]. The patient, however, died 17 days after receiving pembrolizumab. Since the time to response for pembrolizumab is 1.4 to

8.2 months (median, 2.2 months) [9], using pembrolizumab to treat CUPs may be difficult even if the tumour cells show a strong intensity and are 100% positive for PD-L1 expression.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Oxford Medical Case Reports* online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

ETHICAL APPROVAL

No ethical approval was required, as this was a clinical case.

CONSENT

Patient permission was obtained prior to writing this report.

GUARANTOR

Dr Toshiki Ito

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