CASE REPORT

Leukemoid reaction as a paraneoplastic syndrome in hypopharyngeal squamous cell carcinoma with cutaneous metastasis: an exceedingly rare occurrence

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SUMMARY

Head and neck squamous cell carcinoma is considered a locoregional disease, with a distinct chance of metastasis, however, skin is an unusual site. Haematological paraneoplastic syndromes are even rarer, and may be the only presenting feature in these malignancies, producing diagnostic confusion. Cutaneous metastasis, in addition to signifying poor response to treatment and prognosis, can cause diagnostic difficulty if the metastasis is located with an occult primary, and is associated with a higher incidence of multiple synchronous primaries. This article describes a 52-year-old patient with multiple swellings on the left side of the neck and hoarseness of voice. On evaluation, the multiple swellings were found to be cutaneous metastasis from a hypopharyngeal squamous cell carcinoma, with a leukemoid reaction. He opted for palliative radiotherapy and succumbed to his illness within 3 months of presentation. This article discusses the importance of this unusual presentation and diagnostic difficulties associated with it.

BACKGROUND

Cutaneous metastasis from hypopharyngeal squamous cell carcinoma is a rare diagnosis, occurring in <1% of tumours, however, its implications are important; these tumours are aggressive and more often associated with multifocality; they have a poor prognosis, and reduced response to treatment and outcome. They can also cause diagnostic confusion if the primary is occult—necessitating awareness about this unusual occurrence.

Paraneoplastic syndromes in these patients are also exceedingly rare—leukemoid reaction is a haematological paraneoplastic syndrome, hypothesised to be due to activation of humoral stimulation by tumour necrosis-induced blastic factors.

Although rare (to the best of our knowledge, there has been no mention in the literature of both these occurring in the same patient), awareness about these rare presentations is important, especially in geographic areas where these malignancies are extremely common, as haematological disturbances or cutaneous metastatic deposits (often mistaken for other skin conditions) may be the only presenting feature in these patients.

CASE PRESENTATION

A 52-year-old man with a longstanding history of tobacco chewing—over 20 years—presented to us with multiple swellings on the left side of the neck for 2 weeks and progressive hoarseness of voice for 3 months. He had no other relevant medical or familial history of similar or associated illnesses.

On examination, his Eastern Cooperative Oncology Group score was 3. Externally, a diffuse swelling was noted on the left side of his neck, measuring 10×8 cm, with lateral displacement of left sternocleidomastoid belly, with generalised hyperpigmentation of the overlying skin and the presence of six nodules, measuring on average 2–3 mm in diameter ([figure 1](#)). On palpation, the neck mass was hard and fixed. On indirect laryngoscopy, the patient was found to have an ulceroproliferative growth in the left pyriform sinus, suggestive of malignancy. He had no contralateral cervical lymphadenopathy or other signs of metastasis.

INVESTIGATIONS

All routine laboratory tests, except complete blood counts and peripheral smear, were within normal

Figure 1 Clinical photograph showing metastatic nodules on the left side of the neck.

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Figure 2 CT scan of the neck with intravenous contrast showing an irregular lesion arising from the left pyriform fossa, measuring approximately 4×4 cm, heterogeneous enhancement and compression of the laryngeal inlet, with loss of fat planes.

range. His haemoglobin was 10.5 g%, total leucocyte count was 46 490/mm³ (with a differential count of 87% neutrophils and 3% lymphocytes) and platelet count was 375 000/mm³. Peripheral blood smear showed marked neutrophilic leucocytosis with the presence of toxic granules and cytoplasmic vacuoles. Leucocyte alkaline phosphatase staining was used to distinguish it from chronic myeloid leukaemia (although genetic testing for Philadelphia chromosome is ideal, this is an unlikely diagnosis in the setting of neutrophilic leucocytosis).

Chest X-ray and abdominal ultrasonography were normal. CT scan of the neck with intravenous contrast showed an irregular lesion arising from the left pyriform fossa, measuring approximately 4×4 cm, with heterogeneous enhancement, and compressing the laryngeal inlet, with loss of fat planes (figure 2).

Videolaryngoscopy confirmed the presence of an ulceroproliiferative growth in the left pyriform sinus extending into the arytenoid, aryepiglottic fold and more than half of the epiglottis. Ipsilateral vocal cord movement was not discernible. The growth was biopsied, which showed squamous cell carcinoma.

Biopsy of the cutaneous nodule showed intradermal deposit of squamous cell carcinoma (figure 3). The pathological features suggestive of this diagnosis were atypical intradermal keratinocytes with dysplasia, mitotic figures and nuclear pleomorphism, with a mild desmoplastic reaction. Immunohistochemical staining for squamous cell carcinoma and human papilloma virus would have provided additional information, however, it was not performed.

The final diagnosis was squamous cell carcinoma of the left hypopharynx (T3N3M1).

DIFFERENTIAL DIAGNOSIS

- ▶ Lymphoma of the hypopharynx
- ▶ Cutaneous metastasis from malignant melanoma

TREATMENT

In view of metastasis, the patient was offered chemotherapy with palliative radiation to the neck. The patient did not opt for chemotherapy, choosing to receive only palliative radiotherapy.

OUTCOME AND FOLLOW-UP

The patient succumbed to complications of the illness within 3 months of presentation.

Figure 3 Histopathological examination of the cutaneous nodule showing intradermal metastatic deposits of squamous cell carcinoma.

DISCUSSION

Head and neck squamous cell carcinoma is the sixth most common cancer in the world, with an estimated two-thirds of these cases occurring in developing countries due to rampant tobacco use and recently chronic infection with the human papilloma virus. South-east Asian countries, which have the highest incidence, also have a comparatively higher mortality associated with the disease, likely to be due to delay in seeking treatment.¹

It is an aggressive disease with metastasis having been reported in up to 15–20% of cases, with lungs, bone and liver being common sites.² Although cutaneous metastasis occurs in <1% of patients,³ several large studies (the largest having 100 453 patients) on cutaneous metastasis have shown that up to 9% of all cutaneous metastasis occur from head and neck malignancies, the majority of which were squamous cell carcinoma⁴—implying that, in cutaneous metastasis from an unknown primary, head and neck malignancies are important primaries to be considered.

Risk factors for distant metastasis include high-grade tumours, mode of tumour cell invasion⁵ and association with human papilloma virus.⁶ Cutaneous metastases, in particular, are associated with aggressive disease, and poor response to treatment and outcome, with average life-expectancy from time of diagnosis being 4 months.⁷ They are also associated with a higher incidence of synchronous malignancies in the upper aerodigestive tract.⁸ Hence cutaneous metastasis may preclude aggressive treatments.

The histopathological features of squamous cell carcinoma can be diverse, often depending on the degree of differentiation of the tumour.⁹ Presence of invasion of the basement membrane is diagnostic of malignancy; however, the invasion can be in the form of cohesive or dis cohesive aggregates, with variable amounts of desmoplastic reaction. The malignant cells themselves are atypical keratinocytes with dysplasia, mitotic figures and nuclear pleomorphism.¹⁰ Well-differentiated tumours show the presence of keratin pearls; poorly differentiated tumours may lack many of these defining features, and require immunohistochemical staining, such as cytokeratins, to differentiate them from other tumours such as adenocarcinoma and malignant melanoma.¹¹ P16 staining for human papilloma virus-associated carcinomas is of additional interest in oropharyngeal squamous cell carcinomas, with some studies suggesting that human papillomavirus positivity, by virtue of being a good

prognostic factor, may warrant a de-escalation of adjuvant therapy.¹²

Our patient had a leucocyte alkaline phosphatase-negative neutrophilic leucocytosis of over 40 000/mm³, which was suggestive, but not absolute evidence, of a paraneoplastic leukemoid reaction. A detailed clinical examination was carried out, and a chest X-ray, abdominal ultrasound and routine blood investigations (including C reactive protein levels) were ordered to rule out an infective cause for leucocytosis. Regrettably, our evaluation for neutrophilic leukemoid reaction was not exhaustive—we should have tested for the Philadelphia chromosome, performed a bone marrow aspiration and performed a nuclear isotope scan to detect an occult abscess. However, in view of the patient's financial limitations and poor prognosis, we did not perform an extensive diagnostic evaluation. Paraneoplastic syndromes are a diagnosis of exclusion, associated with approximately 7% of all cancers, with incidence in primary head and neck cancers being unknown. These are most commonly endocrine, such as SIADH, hypercalcaemia and gynecomastia, and dermatological manifestations, such as acanthosis nigricans, Bazex syndrome and Sweets syndrome,¹³ with haematological manifestations being exceedingly rare. Nonetheless, they may be important as they might be the first clinical manifestation and could help raise suspicion of an underlying tumour,¹⁴ especially

in high-risk patients who manifest with abnormalities such as anaemia, thrombocytosis, disseminated intravascular coagulation or leukemoid reactions.¹⁵ There are several hypotheses put forward to explain these manifestations, including interference with vitamin B₆ and B₁₂ metabolism, presence of an anti-erythropoietin factor and excessive motivation of humoral stimulation for haemopoiesis by blastic factors produced by tumour necrosis.¹⁶ Although there is no specific treatment described for these associated disorders, awareness is the key to earlier diagnosis and initiation of treatment in these aggressive malignancies.

Contributors BH worked up and diagnosed the case. NS prepared the case report.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- ▶ Cutaneous metastasis from head and neck squamous cell carcinoma is important to be aware of as it may be the only clinical manifestation, and it changes the staging of disease and is associated with poor response to treatment and outcomes.
- ▶ Up to 9% of all cutaneous metastases are from primary head and neck malignancies; in cutaneous metastasis with occult primary, this region should be thoroughly investigated.
- ▶ Paraneoplastic syndromes are rare associations with head and neck malignancies, the commonest manifestations being endocrine or cutaneous.
- ▶ Other unexplained manifestations, such as neuromuscular, rheumatological and ocular manifestations in high-risk patients (males with a history of heavy tobacco abuse), should prompt evaluation for head and neck malignancy when other more common diagnoses producing those symptoms are ruled out.

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