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CASE REPORT

Parathyroid Hormone Related Protein Mediated Hypercalcaemia Due to Metastatic Squamous Cell Carcinoma Originating from Pilonidal Disease: A Case Report

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Abstract

A 56-year-old male presented with a longstanding, gradually enlarging, painful, skin lesion over the natal cleft. This was initially thought to be a pilonidal abscess but, following multiple surgeries, he was diagnosed with Stage IVb squamous cell carcinoma of the natal cleft skin with bilateral inguinal lymph node metastases and subcutaneous metastatic deposits. Complete surgical cure was not possible. He underwent radiotherapy, cisplatin chemotherapy and cemiplimab immunotherapy to control his disease. His course was complicated by severe humoral hypercalcaemia of malignancy (HHM) resistant to medical therapy. His disease progressed, and he developed widespread metastases. He was thus transferred to palliative care with pain control being the major priority. He died within a year of diagnosis.

Key words: metastatic; squamous cell carcinoma; pilonidal disease; hypercalcaemia of malignancy; case report

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Introduction

Parathyroid hormone (PTH) independent hypercalcaemia is seen in 1.2% of patients with squamous cell carcinomas (Nicolae and Schipor, 2010). There are a few reports of humoral hypercalcaemia of malignancy (HHM) associated with primary cutaneous squamous cell carcinoma (SCC) arising from the chest wall, burn scars and decubitus ulcers (Saeed et al, 2017).

We report a rare case of a middle-aged gentleman with HHM secondary to a metastatic skin SCC arising from chronic pilonidal disease. These tumours show a more aggressive behaviour than primary cutaneous SCCs (Safadi et al, 2023). Local defense mechanisms are diminished due to chronic infection and inflammation in chronic pilonidal disease. Fistula tracts provide a pathway for local and systemic metastases and complete surgical removal is often not possible (Safadi et al, 2023).

Case Report

A 56-year-old gentleman presented with a longstanding, 5 cm wide, painful natal cleft mass progressively increasing in size. Surgical incision and drainage

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were performed in November 2022. He represented in January 2023 with poor wound healing and persistent foul-smelling discharge from the surgical site. He re-underwent wide local excision of the natal cleft skin, with dissection extending to the pre-sacral fascia. Histology showed a moderately differentiated keratinizing SCC with an infiltrative depth of 45 mm.

Three months later, he developed bilateral groin lymphadenopathy. Core lymph node biopsies showed metastatic moderately differentiated keratinizing SCC. Computed tomography (CT) confirmed regional metastatic disease confined to bilateral inguinal lymph nodes. Surgical excision of the recurrent SCC and bilateral groin dissection were carried out.

Histology showed a moderately-to-poorly differentiated SCC, measuring 25 mm in the largest dimension and with an infiltrative depth of 9.5 mm. Extensive perineural invasion was noted. Local metastatic disease was confined to inguinal lymph nodes and subcutaneous tissue. The disease was staged as a pT3 pN2 pM1 tumour as per the 8th Edition of the TNM Classification of Malignant Tumours Guideline (Brierley et al, 2017).

During this admission, in May 2023, he developed HHM (Table 1). His electrocardiogram showed a normal QTc interval at 387 ms (Fig. 1). He complained of severe lethargy but denied polydipsia, polyuria, bone pains or constipation. The patient received intravenous 0.9% saline at a rate of 1 L every 8 hours and was administered 4 mg of Zoledronic acid. His calcium level dropped to a nadir of 2.39 mmol/L and he was subsequently discharged.

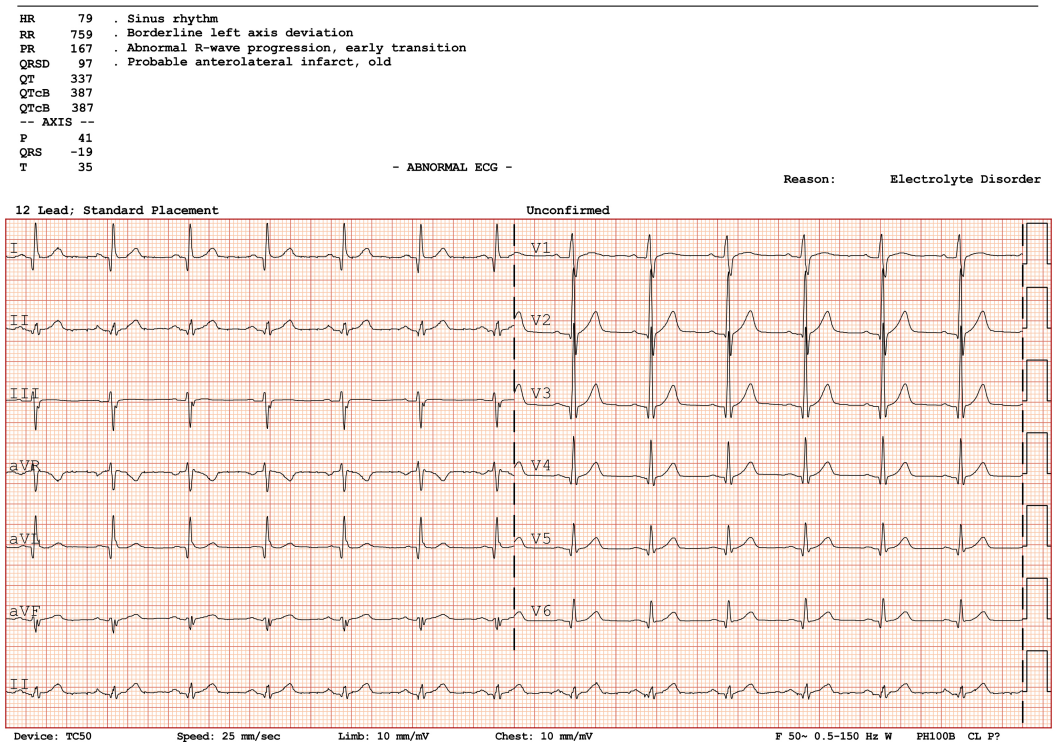

Fig. 1. Electrocardiogram taken during hypocalcaemia. QTc interval is 387 ms.

Table 1. Blood investigations.

Investigation	Result	Reference range
Serum calcium	3.34 mmol/L	2.15–2.55 mmol/L
Serum phosphate	0.6 mmol/L	0.87–1.45 mmol/L
Serum albumin	42 g/L	32–52 g/L
Serum corrected calcium	3.3 mmol/L	2.05–2.6 mmol/L
Creatinine	77 µmol/L	59–104 µmol/L
Estimated glomerular filtration rate (eGFR)	96 mL/min/1.73 m^2	>60 mL/min/1.73 m^2
Parathyroid hormone (PTH)	<0.5 pmol/L	1.96–9.33 pmol/L
Parathyroid hormone related protein (PTHrP)	1.7 pmol/L	<1.3 pmol/L
Serum protein electrophoresis (SPE)	No monoclonal band detected	
25 OH Vitamin D	<13 ng/mL	30–50 ng/mL
1,25-dihydroxy vitamin D	116.63 pmol/L	47.04–130 pmol/L
Serum angiotensin converting enzyme (ACE)	30 U/L	20–70 U/L
Na	135 mmol/L	135–145 mmol/L
K	4.19 mmol/L	3.5–5 mmol/L
Thyroid stimulating hormone (TSH)	1.27 micU/L	0.3–3.15 micU/L
Free thyroxine (T4)	16.2 pmol/L	11.9–20.3 pmol/L
Alanine aminotransferase	17 U/L	5–41 U/L

In July 2023, he was readmitted in view of chronic pain over the left inguinal area and persistent hypercalcaemia. A repeat CT showed multiple enlarged necrotic bilateral external iliac and inguinal lymphadenopathy. No further surgical procedures were possible. Oncology specialists suggested radiotherapy consisting of 55 Gy in 20 fractions to both inguinal areas and 50 Gy in 20 fractions to the natal cleft followed by four cycles of weekly Cisplatin chemotherapy. The hypercalcaemia improved in response to intravenous 0.9% saline (Fig. 2). The lymph nodes decreased in size in response to radiotherapy.

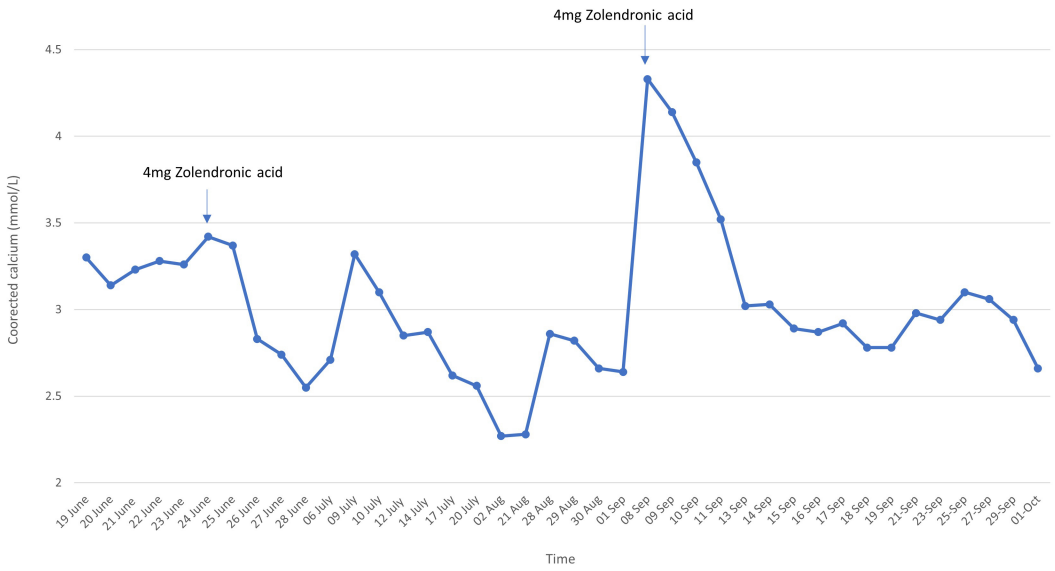

Fig. 2. Variation of corrected Calcium levels vs time.

In September 2023, he complained of worsening inguinal pain and hypercalcaemia. A repeat CT showed pulmonary embolism (Fig. 3a) and progression of his metastatic SCC to the lung, liver and abdominal wall (Fig. 3b–d). Hypercalcaemia was treated with continuous intravenous 0.9% saline replacement. Intravenous Zoledronic acid 4 mg was read ministered on 9th September 2023 (Fig. 2).

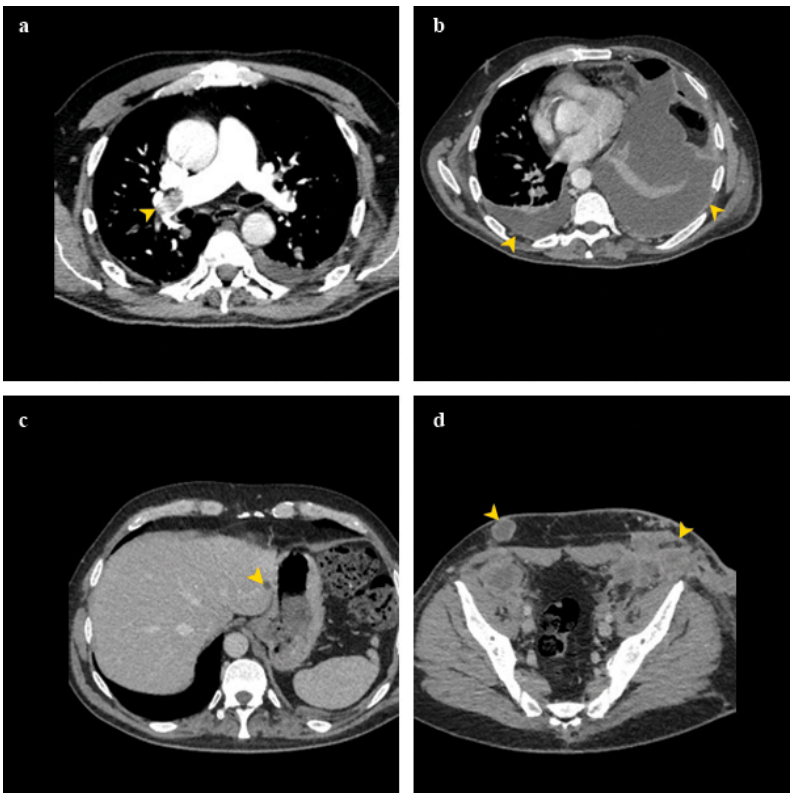

Fig. 3. CT scan showing pulmonary artery filling defect marked by arrow in (a) confirming pulmonary embolism, bilateral pleural effusions marked by arrows in (b), liver metastases marked by arrow in (c) and abdominal wall metastases marked by arrows in (d).

He started palliative Cemiplimab immunotherapy, a treatment approved for metastatic SCC, but developed toxic epidermal necrolysis as a complication. Cemiplimab was thus stopped, and he was treated in a palliative manner. Intravenous fluids and bisphosphonate therapy were given as required to control his hypercalcaemia. He died in October 2023.

Discussion

To our knowledge, this is the first case where an SCC arising from pilonidal sinus disease (PSD) was associated with Parathyroid hormone related protein (PTHrP) mediated hypercalcaemia. PSD affects 5% of the general population (Mayol Oltra et al, 2020) and arises after hair shafts become impacted and penetrate the dermis to produce a foreign body reaction and chronic inflammation. 0.1% of patients with recurrent pilonidal disease develop malignant transformation with a mean duration of over 20 years (Rassi et al, 2020).

All excised specimens of PSD should thus be sent for pathologic examination (Rassi et al, 2020). SCC is the most frequent type of cancer (90%) but basal cell carcinoma, adenocarcinomas and verrucous carcinomas have also been reported. SCC arising from pilonidal sinus is usually seen in males (90%) with a mean age of 50 years (Eryılmaz et al, 2014). Tumours are slow growing but highly invasive (Martino et al, 2011). Inguinal lymphadenopathy at diagnosis is associated with median survival of two years (Mayol Oltra et al, 2020; Safadi et al, 2023). The gold standard treatment is radical excision of the neoplasm with tumour free margins (Martino et al, 2011). Treatment options for unresectable disease include radiotherapy, chemotherapy and immunotherapy (Soria Rivas et al, 2023).

Hypercalcaemia in the setting of malignancy may be due to osteolytic hypercalcaemia, HHM, excess production of 1,25-dihydroxyvitamin D and ectopic PTH secretion. In our case imaging investigations ruled out bone metastases. An elevated level of PTHrP combined with suppressed PTH and normal level of activated vitamin D confirmed the diagnosis of HHM.

HHM occurs due to the secretion of humoral factors in malignant tumours in patients without bone metastases (Asonitis et al, 2019). Complete tumour surgical removal is the treatment of choice. Intravenous fluids increase calcium excretion and bisphosphonates inhibit the apoptosis of osteoblasts and induce the apoptosis of osteoclasts (Asonitis et al, 2019). Other treatment options include calcitonin and denosumab. Calcitonin decreases the resorption of hydroxyapatite from bone and enhances the renal excretion of calcium. Denosumab is a RANKL antibody that inhibits osteoclast maturation, activation, and function.

Learning Points

- We report a unique and novel case of a middle-aged gentleman with HHM secondary to a metastatic skin SCC arising from chronic pilonidal disease malignant transformation of chronic pilonidal disease is rare but after surgical excision samples should always be sent for histological analysis. Early detection improves prognosis in the management of SCC.
- SCCs arising in chronic pilonidal disease show a more aggressive behaviour than primary cutaneous SCCs because local defense mechanisms are diminished due to chronic infection and inflammation in chronic pilonidal disease. In addition, fistula tracts provide a pathway for local and systemic metastases and complete surgical cure is often not possible.
- PTH-independent hypercalcaemia occurs in 1.2% of patients with SCC. This case presents a rare but noteworthy cause of hypercalcaemia in the setting of malignancy. Other causes to keep in mind are osteolytic hypercalcaemia, excess production of 1,25-dihydroxyvitamin D and ectopic PTH secretion.
- HHM should be managed acutely with intravenous fluids, bisphosphonate therapy, calcitonin or denosumab therapy. However, complete surgical removal of the tumour is the only curative approach.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

MG, NM, DP all contributed equally to the data collection and write up. AM made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. MG and NM drafted the manuscript. All authors contributed to important editorial changes of important content in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The patient gave his consent to publish this case report.

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Conflict of Interest

The authors declare no conflict of interest.

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