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REFRACTORY PRURITUS IN END-STAGE PROSTATIC ADENOCARCINOMA: AN UNUSUAL PRESENTATION OF A HYPEREOSINOPHILIC SYNDROME

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ABSTRACT

Introduction: Hypereosinophilic syndrome (HES) associated with advanced adenocarcinoma of the prostate is an exceptionally rare paraneoplastic condition. Available evidence suggests that eosinophilia may correlate with tumour progression and poor prognosis. Cutaneous manifestations, including severe pruritus and angioedaema, may significantly impair quality of life and represent particularly challenging symptoms in a palliative care setting. Pruritus management requires individualised multidisciplinary approaches including corticosteroids, antihistamines, gabapentinoids, antidepressants, opioid modulation and supportive care measures. In refractory cases, severe pruritus associated with HES may become a source of profound suffering and in end-of-life care may require palliative sedation to relieve otherwise intolerable distress.

Case description: We report the case of a patient with prostatic acinar adenocarcinoma who developed paraneoplastic HES, presenting with severe refractory pruritus and recurrent angioedaema. Despite multiple symptomatic treatments, the patient experienced progressive symptom burden with significant impairment in quality of life, ultimately requiring terminal palliative sedation during end-of-life care.

Conclusion: This case highlights the diagnostic challenges of HES, the importance of malignancy progression and the severe impact of uncontrolled eosinophil-mediated symptoms in advanced cancer.

KEYWORDS

Adenocarcinoma of the prostate, hypereosinophilic syndrome, pruritus, palliative sedation

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LEARNING POINTS

- Paraneoplastic hypereosinophilic syndrome should be considered in patients with advanced prostate adenocarcinoma and persistent unexplained eosinophilia after exclusion of allergic, infectious, autoimmune, endocrine and haematologic causes.
- In paraneoplastic hypereosinophilic syndrome, the severity of pruritus may not correlate with peripheral eosinophil counts, and symptom burden can persist despite corticosteroid therapy and normalisation of eosinophilia.
- To our knowledge, this is one of the first reported cases of paraneoplastic hypereosinophilic syndrome secondary to metastatic prostate adenocarcinoma in which refractory pruritus became the indication for palliative sedation.

INTRODUCTION

Hypereosinophilic syndrome (HES) associated with acinar adenocarcinoma of the prostate is an extremely rare condition, reported only rarely in the literature. In most cases, eosinophilia appears to represent a paraneoplastic phenomenon rather than a primary haematologic disorder. Although eosinophilia is more commonly associated with haematologic malignancies, selected solid cancers – including prostate cancer – may occasionally induce marked eosinophilic proliferation through cytokine-mediated mechanisms. Other cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-3 (IL-3), may also contribute[1-4].

The diagnostic workup requires exclusion of primary clonal eosinophilic disorders and secondary causes such as parasitic infections, allergic diseases, drug reactions, autoimmune disorders and adrenal insufficiency[2,3,5,6]. Although the prognostic significance remains uncertain, available reports suggest that marked eosinophilia in prostate cancer is generally associated with advanced disease and poor clinical outcome[4,7]. Reported cases of prostate adenocarcinoma-associated eosinophilia usually involve advanced or metastatic disease with aggressive biological behaviour. Eosinophil counts may parallel tumour burden and disease progression, supporting a tumour-driven mechanism. In several patients, eosinophilia improved after antineoplastic treatment and recurred during disease progression, further suggesting a reactive or paraneoplastic origin[4,7].

The pathophysiology remains incompletely understood, but ectopic production of eosinophilopoietic cytokines, particularly interleukin-5 (IL-5), is considered the main mechanism. Clinically, patients may present with isolated eosinophilia or with full HES associated with organ involvement. Reported manifestations include constitutional symptoms, skin rash, pulmonary infiltrates, dyspnoea, thrombotic events and eosinophilic cardiac damage[2,3]. Persistent unexplained eosinophilia in older adults may occasionally warrant investigation for occult malignancy, including prostate cancer[4,7].

Cutaneous manifestations, particularly severe pruritus and angioedema, may profoundly impair quality of life in patients with advanced cancer. In palliative care settings, pruritus is often multifactorial and may be related to malignancy, drug reactions, organ dysfunction or paraneoplastic syndromes. Management is frequently challenging and may require corticosteroids, antihistamines, gabapentinoids, antidepressants, opioid modulation and supportive measures[8,9]. In rare cases, refractory pruritus may become a source of severe physical and psychological suffering, requiring palliative sedation to relieve otherwise intolerable distress in end-of-life care[8,9].

CASE DESCRIPTION

We describe the case of an 85-year-old male patient, known for stage IV prostatic adenocarcinoma with multiple pulmonary, hepatic and bone metastases, who was admitted to an acute palliative care unit for progressive deterioration of his general condition, characterised by chronic left inguinal pain radiating to the anterior thigh, poorly responsive to standard analgesics and asthaenia. Associated symptoms included weight loss and constipation.

During hospitalisation, analgesic therapy with intravenous hydromorphone was initiated, titrated and subsequently converted to an enteral formulation. Ten days after admission, the patient developed a rapid onset of right periorbital oedema in the absence of other systemic symptoms; ophthalmological evaluation ruled out infectious and thrombotic causes, and treatment with topical corticosteroids led to a prompt resolution of the condition. Subsequently, laboratory investigations revealed marked and persistent hypereosinophilia (>3 g/l; normal value < 0.7 g/l) associated with generalised pruritus, which rapidly became the predominant and most distressing symptom. Due to the close temporal relationship between the switch from intravenous hydromorphone to its oral formulation and the onset of symptoms, an allergic reaction was initially suspected, possibly related to an excipient present in the tablet formulation. However, further investigations – including serum tryptase levels and anti-gelatin antibody testing – were negative, making an allergic reaction unlikely. A subsequent drug-induced reaction (non-allergic) was then considered. For this reason, oral hydromorphone was discontinued and the analgesic regimen was completely changed, replacing it with intravenous fentanyl. High-dose corticosteroid therapy was also initiated (5 mg/kg). A comprehensive diagnostic workup was performed,

including autoimmune screening, cortisol level and a peripheral blood smear. All examinations were normal; the blood smear excluded dysplastic features, and no evidence of haematological malignancy was identified. In the absence of a cutaneous rash, liver and renal involvement, a drug reaction with eosinophilia and systemic symptoms was also excluded. A skin biopsy was discussed, but in consideration of the advanced oncological condition and the progressive decline of the patient, this was deemed not appropriate.

Despite a progressive reduction of eosinophil counts over the following weeks, the patient experienced persistent and severe pruritus, that was unresponsive to several pharmacological trials with antihistamines, duloxetine and gabapentin, prescribed according to the available literature[8].

In the absence of alternative aetiologies and considering the oncological context, the condition was interpreted as a paraneoplastic hypereosinophilic syndrome associated with an end-stage prostatic cancer.

The clinical course was marked by a progressive functional decline and a worsening symptom burden. Pruritus became intolerable and refractory, leading to diffuse abrasions and severe psycho-existential distress. Multiple interprofessional meetings with patient and family facilitated shared decision-making on the management of the terminal phase and palliative sedation was started, in consideration of refractory suffering.

DISCUSSION

Hypereosinophilic syndrome associated with prostate adenocarcinoma is an exceptionally rare paraneoplastic phenomenon, with only isolated cases reported in the literature. In most published reports, eosinophilia occurs in the setting of advanced or metastatic disease and appears to correlate with tumour progression and an unfavourable prognosis.

In this case, extensive investigations excluded the most common secondary causes of eosinophilia including allergic, autoimmune, infectious, endocrine and haematologic disorders. Although an initial drug-related reaction was considered because of the temporal association with oral hydromorphone administration, the absence of supportive laboratory findings and the persistence of symptoms despite opioid discontinuation made this hypothesis less likely. Paraneoplastic hypereosinophilic syndrome was considered as the most probable diagnosis in this context.

The most remarkable aspect of this case was the severity and refractoriness of pruritus, which became the predominant source of suffering during the patient's terminal phase. Pruritus in hypereosinophilic syndromes is often multifactorial and may result from eosinophilic infiltration of the skin, eosinophil degranulation, and release of pro-inflammatory and neuroactive mediators capable of activating peripheral itch pathways.

Importantly in our patient, reduction of eosinophil counts after corticosteroid therapy did not translate into meaningful clinical improvement of pruritus. This observation suggests that symptom severity may not directly correlate with peripheral eosinophil levels and highlights the complexity of itch mechanisms in paraneoplastic eosinophilic syndromes. Despite treatment with corticosteroids, antihistamines, gabapentin, duloxetine and opioid rotation, the patient continued to experience intolerable generalised pruritus associated with excoriations, insomnia, agitation and severe psycho-existential distress.

Pruritus is frequently underestimated in palliative care despite its major impact on quality of life. Severe chronic itch may lead to sleep deprivation, anxiety, depression, social isolation and loss of dignity, becoming comparable to uncontrolled pain in terms of global suffering. Management is often challenging because evidence-based therapeutic strategies remain limited, especially in paraneoplastic and eosinophilic conditions. Multidisciplinary approaches integrating pharmacologic and supportive interventions are therefore essential.

In this case, refractory pruritus ultimately fulfilled the criteria for a refractory symptom in palliative care. After multidisciplinary evaluation and shared decision-making with the patient and family, palliative sedation was initiated to relieve otherwise intolerable suffering during end-of-life care.

CONCLUSION

To our knowledge, reports describing refractory paraneoplastic pruritus requiring terminal sedation are exceedingly rare.

This case highlights the rare association between metastatic acinar adenocarcinoma of the prostate and paraneoplastic hypereosinophilic syndrome. Persistent unexplained eosinophilia in patients with advanced malignancy should prompt consideration of a paraneoplastic mechanism after exclusion of alternative causes.

This case also underscores the potentially devastating impact of pruritus in palliative care patients. Although often considered as a secondary symptom, severe pruritus may become a major determinant of suffering and profoundly compromise quality of life.

Management of refractory pruritus in hypereosinophilic syndromes requires an individualised multidisciplinary approach. In exceptional cases, when symptom burden remains intolerable despite maximal conventional therapy, palliative sedation may represent an ethically appropriate intervention aimed at relieving otherwise refractory suffering at the end of life. Further research is needed to establish evidence-based therapeutic strategies and standardised assessment tools for eosinophilia-related pruritus in specialist palliative care settings.

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