Post-radiotherapy cutaneous mastocytosis

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Abstract
We present the case of a 50-year-old female patient with a history of breast cancer, previously treated with radiotherapy, who presented with a localised petechial rash in the left chest wall skin. Histological examination revealed an infiltrate of c-KIT positive mast cells and a diagnosis of cutaneous mastocytosis was made. In the literature there have been very few reported cases of mastocytosis within irradiated areas, all of which have occurred in the context of adjuvant radiotherapy for breast cancer.

Keywords c-KIT; radiotherapy; rash; systemic mastocytosis

Case report
A 50-year-old female patient presented with a localised petechial rash in the left chest wall skin (Figure 1). The patient had a past history of breast cancer and had undergone a left mastectomy and radiotherapy 15 months prior to presentation.

A punch biopsy of the rash was performed. Microscopically the epidermis showed increased basal pigmentation, and an interstitial and perivascular loosely distributed infiltrate of mast cells with small numbers of eosinophils (Figure 2a). The mast cells stained positively with CD25 and c-KIT (Figure 2b) and a diagnosis of cutaneous mastocytosis was made. Targeted sequence analysis of c-KIT exons 13 and 17 detected no mutations. However, the percentage of tumour cell nuclei estimated within the area from which DNA was extracted was below the limit of detection for Sanger sequencing. Analysis of c-KIT exons 9 and 11 failed to produce a result despite repeated testing.

The patient was then found to have an elevated serum tryptase of 21.7 ng/ml, suggesting systemic mastocytosis, although at first, she had presented with no systemic symptoms.

A bone marrow aspirate was then taken which showed hypercellular marrow with focal aggregates of spindled mast cells. Flow cytometry revealed mast cells to be 0.04% of total cells with a neoplastic phenotype and a diagnosis of systemic mastocytosis was then made.

Discussion
Cutaneous mastocytosis presenting during adulthood appears to endure for the duration of life. The diagnosis proves a challenge as the features can be subtle, and the mast cell infiltrate may be slight. A large series1 has proposed that in all, and demonstrated that in most (n=57, 97%), of these cases patients have systemic mastocytosis with cutaneous involvement. The WHO classification splits mastocytosis into cutaneous mastocytosis, systemic mastocytosis and localised mast cell tumours.2 The WHO criteria for diagnosis of systemic mastocytosis are to detect either one major and at least one minor criterion, or three minor criteria (Table 1). The oncogenic KIT mutation D816V in exon 11 is detectable in >80% of all patients with systemic mastocytosis.2

Subsequently the patient was then found to have mild symptoms of systemic mastocytosis including abdominal bloating, occasional bladder incontinence and bone pain. Her symptoms have been subsequently managed well with fexofenadine as well as the patient now carrying an EpiPen.

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The difference between prognosis in cutaneous mastocytosis and systemic mastocytosis renders the distinction in diagnosis and the choice of intervention important. A literature search has revealed only six cases of mastocytosis within irradiated areas. All of these occurred in female patients, aged between 43 and 62 years, in the context of adjuvant radiotherapy post-surgery for breast cancer. The radiotherapy to rash interval ranged from 3 to 24 months. The first described case was in 1971, and the diagnosis was delayed. This delay was thought to be due to the excess in mast cells found immediately after ionising radiation, and that there was no previous literature of this Koebner-like effect post-radiotherapy. In another case the delay was due to confusion over whether the rash represented a recurrence. In our case, the biopsy was sent to exclude recurrence. Initially the microscopic appearance was thought to be non-specific, until review by a dermatopathologist. The rashes appear similar in the clinical photography published but have been described differently. The rash varies from being described as small, erythematous, scaly lesions, to multiple red-brown macules. In some of the cases the rash is described as extending beyond the radiotherapy field. In our case the patient has retained her rash symptoms despite current therapy, whereas in another case the rash resolved by three years post-diagnosis and after the discontinuation of treatment with antihistamines. All of the cases described had the same microscopic appearance, with a localised increase in mast cells in the dermis being the only distinctive feature, staining positively with toluidine blue, mast-cell tryptase and c-KIT. One case in literature met the criteria for systemic mastocytosis (elevated serum tryptase and KIT D816V mutation). Two other cases had serum tryptase measured but did not meet the criteria. The differences between the patterns seen in the patients described in literature raises the question whether radiotherapy has induced prior asymptomatic, undiagnosed systemic mastocytosis to become symptomatic, whether radiotherapy induced focal cutaneous changes that subsequently resolved, and whether radiotherapy induced systemic mastocytosis via mutations. Due to the historical nature of many of the cases described, it is not possible to test this hypothesis until further cases are described that undergo molecular testing and a full clinical work up.

**Conclusion**

Mastocytosis is an uncommon condition characterized by the accumulation of mast cells within tissue that can be classified as cutaneous or systemic dependent on the WHO diagnostic criteria. This case highlights a presentation of mastocytosis in the context of previous radiotherapy for breast cancer. Although very rare, it is important to be aware of this diagnosis for patients presenting with rashes after radiotherapy for breast cancer.

**Practice points**

- It is important to consider mastocytosis in all rashes following radiotherapy in patients with breast cancer.
- Cases in the literature show a mixture of cutaneous and systemic mastocytosis presentations.
- All such cases of cutaneous mastocytosis should be investigated for systemic mastocytosis.

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**WHO criteria for systemic mastocytosis**

| Major criterion | Multifocal dense infiltrates of mast cells (>15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s) |
| Minor criterion | >25% of all mast cells are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in mast cell infiltrates detected on sections of visceral organs |
| | KIT point mutation at codon 816 in the bone marrow or another extracutaneous organ |
| | Mast cells in bone marrow or blood or another extracutaneous organ exhibit CD2 and/or CD25 |
| | Baseline serum tryptase level >20 ng/ml |

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**Table 1**
Self-assessment multiple choice questions

1. What is the most common mutation present in mastocytosis?
   A. c-KIT D816V
   B. BRAF V600E
   C. c-KIT D419del
   D. PIK3CA H1047R
   E. c-KIT V654A
   
   Answer A.

2. Which of the following is a major diagnostic criterion for systemic mastocytosis?
   A. Tissue infiltrates of 15 or more mast cells per aggregate
   B. Baseline serum tryptase > 10 ng/ml
   C. Tissue infiltrates of mast cells with CD2 positive staining
   D. Tissue infiltrates of mast cells with CD25 positive staining
   E. Tissue infiltrates of 50 or more mast cells
   
   Answer A.

3. Which of the following stains would not be informative to diagnose cutaneous mastocytosis?
   A. c-KIT
   B. Toluidine blue
   C. CD117
   D. CD17
   E. Mast-cell tryptase
   
   Answer D.

REFERENCES