Chronic myelomonocytic leukaemia: leukaemia cutis predicts disease progression

Introduction

Chronic myelomonocytic leukaemia is a myeloid neoplasm with features of myelodysplastic syndromes and myeloproliferative disorders. It often presents with sustained (>3 months) peripheral blood monocytosis (≥1×10^9/litre, monocytes ≥10% of white blood cell count) along with dysplastic features in bone marrow and has an inherent risk of transformation to acute myeloid leukaemia.

Chronic myelomonocytic leukaemia is subdivided into three types (0, 1, 2) depending on the number of blasts and promonocytes which are found in peripheral blood or bone marrow (Patnaik and Tefferi, 2018). Cutaneous manifestations of chronic myelomonocytic leukaemia can be both specific and non-specific (e.g. opportunistic infections, neutrophilic and granulomatous dermatoses, and drug reactions).

The term 'leukaemia cutis' refers to the specific cutaneous manifestations (direct invasion of malignant myeloid blasts into the skin) which occur in 10–15% of patients with acute myeloid leukaemia but less frequently in those with chronic myeloproliferative diseases (Cho-Vega et al, 2008), especially chronic myelomonocytic leukaemia. This article reports two patients with chronic myelomonocytic leukaemia and leukaemia cutis.

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CASE REPORT 1

In October 2016, a 58-year-old woman was admitted to the authors' department with a 4-week history of dizziness and fatigue, and a gradual onset over 10 days of scattered red cutaneous nodules on the chest and upper back (*Figures 1a* and *b*). A complete blood count showed white blood cell count 68.82×10^9/litre, monocytes 54.3×10^9/litre, neutrophils 10.3 ×10^9/litre, red blood cell count 2.49×10^{12}/litre, haemoglobin 83 g/litre and platelet count 76×10^9/litre. The bone marrow smear showed a predominant population of monocytes, including 57.5% dysplastic mature monocytes and 18.5% immature monocytes (*Figure 1c*), consistent with chronic myelomonocytic leukaemia type 2.

Examination of fine needle aspiration of a nodular lesion showed diffuse pleomorphic cells infiltrating into the dermis, mainly primitive and immature monocytes (*Figure 1d*), which was consistent with leukaemia cutis. Conventional cytogenetic studies revealed a diploid female karyotype, 46, XX. The gene mutation TET2 was positive, other mutated genes that can be detected and BCR-ABL fusion gene were negative. The patient was treated with hydroxyurea (1000 mg orally twice daily d1–10) and decitabine (20 mg/m^2 intravenous d1–5, monthly), which caused initial regression of the skin lesions (white blood cell count <10×10^9/litre). However, after 2 weeks the skin lesions reappeared and diffuse red nodules covered the back (*Figure 1e*).

A new bone marrow aspiration showed 70.5% monocytes and 3% promyelocytes, consistent with a diagnosis of acute myeloid leukaemia M5 (*Figure 1f*). The patient was treated with idarubicin 10 mg intravenous d1–3 and cytarabine 100 mg intravenous every 12 hours d1–7), but the lesions were resistant to this new chemotherapy. The patient complained of aggravation of weakness, dizziness and anorexia, and died at home at 3 months after diagnosis.

CASE REPORT 2

In March 2018, a 62-year-old woman was referred to the authors' department with an 8-week history of fatigue and 7 days of diffuse petechial rash on the right limbs (*Figures 2a* and *b*). The patient had taken loratadine and moxifloxacin for 1 week without any change in the skin lesions. Fine needle aspiration of the skin lesions showed atypical monocytes with abundant cytoplasm and irregular nuclei (*Figure 2c*), which lead to a diagnosis of leukaemia cutis. A full blood count showed white blood cell count 107.58×10^9/litre with 93.6×10^9/litre monocytes, 9.6×10^9/litre neutrophils, haemoglobin 97 g/litre, and platelet count 85×10^9/litre. The bone marrow smear showed a predominant population of monocytes, including 88.5% dysplastic mature monocytes and 3% immature monocytes (*Figure 2d*), consistent with a diagnosis of chronic myelomonocytic leukaemia type 0.

Cytogenetic studies revealed normal 46 XX karyotype in two metaphases examined. BCR-ABL fusion gene and gene mutations were negative. The patient was treated with hydroxyurea (1000 mg orally twice daily d1–10) and decitabine (20 mg/m^2 intravenous d1–5, monthly), which led to complete disappearance of the skin lesions in 10 days (*Figures 2e* and *f*). The patient was then in a stable clinical and haematological condition for 4 months.

During the fifth cycle, a bone marrow smear showed 30.5% monocytes and 2% promyelocytes, consistent with a transformation to acute myeloid leukaemia M5 (*Figure 2g*). The patient died of gastrointestinal bleeding 8 months after diagnosis.

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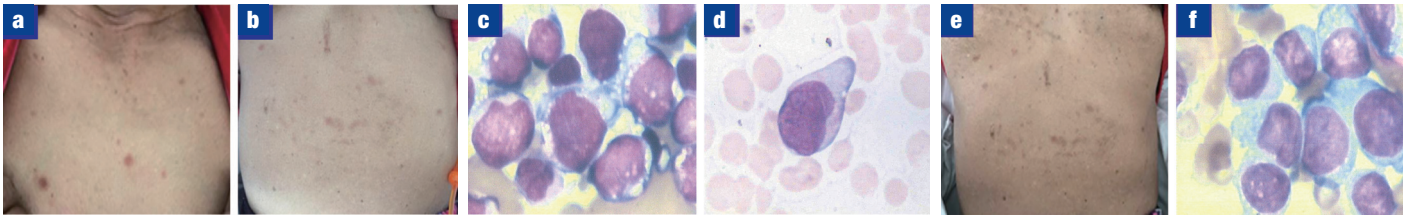

Figure 1. **a** and **b.** Diffuse eruption of rufous nodules and papules on the chest and upper back. **c.** Bone marrow smears showed hyperactive hyperplasia, predominantly abnormal monocytic dysplasia. **d.** A needle puncture of the nodules at high magnification. **e.** Numerous nodules on the back after chemotherapy. **f.** Bone marrow was aspirated again after treatment showing transformation to acute myeloid leukaemia-M5.

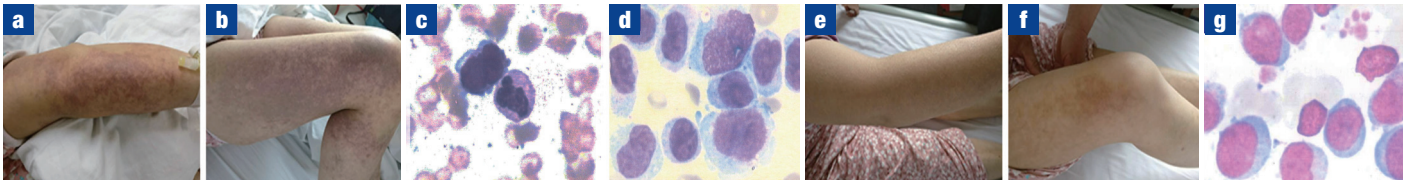

Figure 2. **a** and **b.** Scattered purpuric lesions on the right limbs. **c.** A needle puncture of the nodules at high magnification. **d.** Bone marrow smears showed predominant population of monocytes. **e** and **f.** The skin lesions almost completely disappeared after chemotherapy. **g.** Bone marrow was aspirated again after treatment showing transformation to acute myeloid leukaemia-M5.

Discussion

Leukaemia cutis has been described as a specific lesion in chronic myelomonocytic leukaemia in sporadic case studies (Zhu et al, 2016; Claßen et al, 2018). The majority of cases in the literature presented as localized or disseminated nodules, papules or plaques of varying sizes, while pruritic rash, pustules and ulcers were less common (Martínez-Leboráns et al, 2016). The skin lesions were located anywhere on the body, mostly on the trunk and extremities, followed by the face, arms, chest and scalp (Vitte et al, 2012).

In most cases, cutaneous leukaemic infiltration indicates that the disease will progress within a few months of the diagnosis of leukaemia cutis (Osio et al, 2015; Peña-Romero et al, 2016). Both the current patients had a short time from diagnosis to death.

Both had normal karyotypes and only the first patient was positive for the TET2 mutations. However, TET2 mutations generally have a favourable prognostic significance in chronic myelomonocytic leukaemia with the absence of ASXL1 mutations (Patnaik et al, 2016), which suggests that leukaemia cutis has prognostic significance for disease progression. As an invasion of malignant myeloid cells into the skin, the histological differential diagnosis of leukaemia cutis depends on the morphological and immunohistochemical features of the infiltrative tumour cells (Cho-Vega et al, 2008).

Cutaneous manifestations of chronic myelomonocytic leukaemia exhibit heterogeneous histopathological features. In the largest reported series of leukaemia cutis in chronic myelomonocytic leukaemia, such infiltration of the skin manifests as cutaneous nodules or papules composed of blastic cells showing either granulocytic and monocytic differentiation or dendritic cell lineages. The authors also proposed that plasmacytoid dendritic cells play an important role in the spectrum of lesions (Vitte et al, 2012). When the skin lesions first appeared in these patients, the authors only performed fine needle aspiration cytology of the nodules. These cases remind physicians of the importance of skin biopsy if similar cases are encountered.

Conclusions

Leukaemia cutis is a rare manifestation of chronic myelomonocytic leukaemia associated with imminent leukaemic transformation. A skin biopsy is mandatory to differentiate between specific (malignant) and non-specific (non-malignant) lesions. **BJHM**

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LEARNING POINTS

- Leukaemia cutis may be a predictor of leukaemic transformation in chronic myelomonocytic leukaemia and is associated with a poor prognosis.
- Skin biopsy and further immunohistochemical examination are essential for diagnosis of leukaemia cutis.
- Early diagnosis and accurate identification of leukaemia cutis in chronic myelomonocytic leukaemia has important therapeutic and prognostic significance.

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