Subcutaneous tumours as a harbinger of acute myeloid leukaemia recurrence

Aleksandra Dańczak-Pazdrowska¹, Lidia Gil², Anna Sadowska¹, Karolina Kniola¹, Mieczysław Komarnicki²

¹Department of Dermatology, Medical University of Poznan, Poland
Head: Prof. Wojciech Silny MD, PhD

²Department of Haematology, Medical University of Poznan, Poland
Head: Prof. Mieczysław Komarnicki MD, PhD

Abstract

Skin lesions may suggest the recurrence of haematopoietic neoplasia. Cutaneous manifestations in leukaemia are divided into specific (leukaemia cutis, leukaemic vasculitis) and non-specific (leukaemids). Non-specific lesions may cause diagnostic difficulties due to their diversity. This paper presents two patients with acute myeloid leukaemia with skin lesions presented as tumours located in subcutaneous tissue. In both cases skin lesions preceded the recurrence of the haematopoietic neoplasia.

Key words: acute myeloid leukaemia, relapse, skin symptoms of haematopoietic neoplasia.

Introduction

Acute myeloid leukaemia (AML) is a heterogeneous group of disorders characterized by uncontrolled clonal proliferation of neoplastic precursor cells, leading to impaired haematopoiesis. It constitutes about 30% of all leukemias and 80% of acute leukemias in adults. The overall incidence is 3.4 cases per 100 000 population per year. The median age at diagnosis is approximately 68 years, with increasing incidence with advancing age [1].

Current treatment of AML with standard induction therapy (cytarabine and anthracycline) allows complete remission to be achieved in 60-80% of adults under the age of 55-60 years. Five-year survival is seen in 30-50% of patients treated during the post-remission period with high-dose cytarabine or allogeneic haematopoietic stem cell transplantation (alloHSCT), according to the cytogenetic and molecular risk group [2, 3].

The main cause of treatment failure in patients with AML is relapse, which occurs within 1-2 years after therapy. Resistance to chemotherapy and increased risk of toxic and infectious complications after treatment are observed in this group of patients. An important issue is a delay in diagnosis and treatment caused by an atypical clinical picture of AML relapse. This uncommon clinical picture applies in particular to patients with relapse after HSCT, where involvement of extramedullary tissues can be observed, preceding AML haematological features [3].

We present two cases of patients with relapse of AML after alloHSCT with cutaneous manifestation.

Case 1

We present a case of a 32-year-old woman, treated at the Department of Haematology of Medical University of Poznan.

In 2003, the patient was diagnosed with AML-M2 with intermediate cytogenetic risk. Shortly before the diagnosis the patient complained of increasing weakness and recurrent respiratory infections. The trilineage cytopenia was the indication for haematological assessment. After diagnosis was established, standard induction treatment and consolidation therapy were applied. Because no human lymphocyte antigen (HLA)-identical sibling donor was found, in the first complete remission high-dose chemotherapy and autologous stem cell transplantation were applied. In September 2004, AML relapse occurred. The haematological diagnosis showed the same AML subtype with a normal karyotype. The second complete remission was achieved after FLAG (fludarabine, cytarabine, granulocyte growth factor) chemotherapy, tailored for refractory or recurrent disease. Repeated and extended...
HLA testing among the patient’s family members revealed full HLA compatibility between the patient and her father. AlloHSCT was performed and the patient remained in complete remission with full donor chimerism until January 2007. The second relapse was recognized on the basis of the haematological diagnosis and it had the same characteristics as the previous one. The patient underwent further chemotherapy with the FLAG regimen and achieved the third complete remission. The second alloHSCT from the same donor was performed without complications.

In September 2009, at the Department of Otolaryngology the patient underwent surgery because of a nasal cavity tumour and histological assessment revealed leukaemic infiltration. Further diagnostic tests were performed at the Department of Haematology and confirmed subsequent relapse despite normal blood counts. Bone marrow analysis with immunophenotyping revealed: myeloblasts accounted for 81.9% of nucleated bone marrow cells (CD13 – 0.7%, CD33 – 78%, CD34 – 85% CD117 – 99%, HLA-DR – 54.0% [mean expression], CD15 – 9.7%, CD11b – 0.0%, CD14 – 0.0%, CD38 – 31.0%, MPO – 0.2%, TdT – 0.0%, Ki67 – 64.0%, CD7 – 28.0% [weak expression], CD2 – 0.0%, CD3 – 0.0%, CD4 – 0.0%, CD8 – 0.0%, CD5 – 0.0%, CD19 – 0.0%). Cytogenetic analysis revealed complex (> 3) chromosomal changes. Additionally, the patient developed a number of tumours located deep in the subcutaneous tissue, which occurred 3 months before hospitalization. The tumours were 0.5 to 2 cm in size. Except for one, the lesions were palpable, with no visible skin changes. They were scattered around the subcutaneous tissue of the breasts, abdomen, arms and back. On the skin of the left lumbar area a few clustered, violet, dome-shaped tumours were present (Fig. 1). The tumours were 1-3 cm in size and were tender on palpation. Fine needle biopsy with immunophenotype assessment confirmed their leukaemoid nature: myeloblasts accounted for 92.3% (CD13 – 8.5%, CD33 – 99.5%, CD34 – 100.0%, CD117 – 100.0%, HLA-DR – 98.1%, CD14 – 0.0%, CD38 – 99.2%, MPO – 7.6%, TdT – 27.6%, Ki67 – 21.7%, CD7 – 21.0% [weak expression], CD3 – 0.0%, CD4 – 0.0%, CD8 – 0.0%, cytCD3 – 0.0%, CD19 – 0.0%). The tumours and subcutaneous nodules were visualized on the computed tomography (CT) of the chest and abdomen. There were no other abnormalities observed on CT scan (Fig. 2). The central nervous system was not involved.

In treatment FLAG-Ida (FLAG-idarubicin) chemotherapy was applied, but infectious and toxic complications occurred shortly after therapy. The patient died with multiorgan failure.

Case 2

We present a case of a 38-year-old patient with AML M1 with intermediate risk (normal karyotype). The diagnosis was established in 2007. Before the diagnosis the patient suffered from weakness and skin bleeding diathesis. After the diagnosis was established, the patient was treated with standard induction and consolidation chemotherapy, recommended by the Polish Adult Leukemia Group (PALG). In August 2007, high-dose chemotherapy and alloHSCT from his sister identical in HLA antigens was performed. Until February 2010, the patient remained under the care of the Transplant Outpatient Clinic, with no symptoms of the disease. However, severe herpes zoster infection occurred. In March 2010, the patient was diagnosed at the Neurology Department because of persistent pain and progressive muscle weakness of the right upper limb. Sonography of subcutaneous tissue revealed a tumour mass 55 × 26 mm inside the right armpit. At the same time, on the left side of the neck and the right subclavian area, two soft, painless tumours of approximately 1.5 cm in diameter in the subcutaneous tissue were found. Overlying skin was not pathologically altered (Fig. 3). On the mucous membranes there had been no eruptions. Further research conducted at the Department of Haematology showed AML relapse with the presence of 46.6% myeloblasts in the bone marrow (CD13 – 98.00%, CD33 – 95%, CD34 – 96%, CD117 – 96%, HLA-DR – 98%, CD15 – 3.0%, CD11b – 1.7%, MPO – 1.5%, cytCD3 – 0.0%, TdT – 95.0%, CD7 – 89.4%, CD19 – 0.0%). The biopsy of the skin lesion revealed 98.2% myeloblasts of the phenotype: CD13 – 100%, CD33 – 98%, CD34 – 100%, CD117 – 100% HLA-DR – 97%, CD15 – 0.5%, CD11b – 0.0% MPO, cytCD3 – 0.0%, TAD – 96%, Ki67 – 63%, CD7 – 97%, CD19 – 0.0%. The patient’s blood morphology showed no abnormalities. However, the central nervous system was affected by leukaemia, which was confirmed by the examination of cerebrospinal fluid (62% myeloblasts phenotype ibid.) and CT of the head. Chest X-ray and abdominal sonography showed no significant deviations.

The patient received FLAG chemotherapy without complications. A rapid decline in skin infiltration was observed. The patient remains under the Haematology treatment.
Department’s care and the second allogeneic haematopoietic stem cell transplantation is planned.

Discussion

The most common clinical AML symptoms include infections due to neutropenia, weakness associated with increasing anaemia and thrombocytopenic bleeding disorder. The symptoms usually appear suddenly and increase rapidly. Among other complaints fatigue, weight loss, fever, and bone pain are very common. Occasionally patients present with symptoms resulting from leukaemic infiltrates of soft tissues, including the skin [4].

Skin lesions occurring in the course of leukaemia can be divided into specific (leukaemia of the skin, leukaemic vasculitis) and non-specific, which are called leukaemids [5-7]. The period between diagnosis of the disease and the appearance of skin lesions that is given in the literature ranges from 0 to 13 months [8]. In some cases, they may be a harbinger of ongoing neoplasia [7, 9].

Specific changes are noted less often than non-specific ones. They are observed usually in the course of chronic myelogenous or lymphoblastic leukaemia, and in the group of patients with AML-M4 and AML-M5. They usually present as cohesive, dome-shaped papules or nodules covered with red, purple or dark brown skin. Occasionally they are ulcerated. Usually they are not accom-
panied by subjective symptoms. Such changes are in fact skin metastases. The leukaemic cells infiltrating the skin and surrounding blood vessels may cause leukaemic vasculitis [6, 10-13]. Non-specific changes are reported more often than specific ones. The rate of occurrence is estimated at approximately 80% of patients with leukaemia [5]. Non-specific changes are frequently observed in chronic myeloid and lymphoblastic leukaemia, rarely in the acute forms [12]. These eruptions are associated with systemic abnormalities in the course of the disease or they are just a paraneoplastic phenomenon. The spectrum of its clinical presentations includes focal hyperpigmentation of the skin, generalized itching, urticaria, purpura, sarsoidosis, erythema multiforme, erythema nodosum and other forms of subcutaneous tissue inflammation, Sweet’s syndrome, and pyoderma gangrenosum. They may also imitate drug reactions; however, the chemotherapy and antibiotic therapy used in this group of patients solely may have a tendency to cause real drug reactions [7, 12, 14]. The basis for the differential diagnosis of specific and non-specific changes is the histological examination. In the biopsy specimens of specific changes, unlike non-specific ones, leukaemic cells are found. There are sometimes significant morphological differences between tumour cells infiltrating the skin and neoplastic cells in peripheral blood or bone marrow [15, 16]. A flow cytometry test of skin biopsy specimens is also necessary [7, 15]. Of note, a skin biopsy should be taken from the central part of the skin lesion, where one can find more neoplastic cells than in the marginal part. However, usually it is impossible to recognize the type of leukaemia on the basis of histopathological examination of the skin. A thorough examination of peripheral blood and bone marrow is necessary for proper classification of the disease. In each of the presented cases, leukaemic cells were demonstrated in biopsies from skin lesions, which allows them to be qualified as specific changes.

In the literature we found a few cases in which skin lesions were a harbinger of recurrence of neoplasia of the haematopoietic system. It is suggested that the diagnosis of such eruptions may be an adverse prognostic factor and death occurs usually within a few months after the appearance of skin lesions [8, 10, 17-19]. The presented cases unfortunately confirm that these patients belong to the chemoresistant group, associated with a higher risk of death. In the first of the described cases the patient died within one month after the appearance of skin eruptions.

The authors would like to emphasize that the credibly broad and heterogeneous spectrum of skin lesions observed in the course of leukaemia can lead to delay in making a correct diagnosis, which is particularly disadvantageous since it implies a worse prognosis in this group of patients. Any suspicious skin change requires the implementation of a broad diagnosis, including radiological and histological examinations.

References