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Xiangdong Xu
Washington University School of Medicine in St. Louis
Friederike H. Kreisel
Washington University School of Medicine in St. Louis
John L. Frater
Washington University School of Medicine in St. Louis
Anjum Hassan
Washington University School of Medicine in St. Louis

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Case Report

Mast cell leukemia with prolonged survival on PKC412/midostaurin

Xiangdong Xu[1,2], Friederike H Kreisel[2], John L Frater[2], Anjum Hassan[2]

[1]Department of Pathology, School of Medicine, University of California, San Diego; VA San Diego Healthcare System, San Diego CA, USA; [2]Department of Pathology and Immunology, School of Medicine, Washington University, St. Louis MO, USA

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Abstract: Mast cell leukemia (MCL) is a rare and aggressive form of systemic mastocytosis. There are approximately 50 reported cases since 1950s. MCL is refractory to cytoreduction chemotherapy and the average survival is only six months. We report a MCL case in a 71 year-old woman with high tumor load at the initial presentation in 2005, who did not respond to either interleukin-2 or dasatinib therapy. After enrolled in a clinical trial of PKC412 (or Midostaurin) with a daily dose of 100 mg, the patient responded well to PKC412 and became transfusion independent in three months. Since then, her disease had been stably controlled. This is the first report of a high-tumor-load MCL case which achieved prolonged survival (101 months) by PKC 412. The 101-month overall survival is the longest among reported MCL cases in the English literature.

Keywords: Mast cell leukemia, aleukemic variant, c-kit, D816V, PKC412, Midostaurin, prolonged survival

Introduction

Mastocytosis is a heterogeneous group of disorders with clonal proliferation of mast cells. Mast cell leukemia (MCL) is a rare and aggressive variant of systemic mastocytosis (SM) and comprises approximately 1% of all mastocytosis cases. There are approximately 50 MCL cases reported since 1950s, most of which are single case reports [1]. According to the WHO classification, MCL diagnosis need to first meet the criteria of SM, in addition to diffuse infiltration of bone marrow with at least 20% atypical mast cells [2].

MCL may present de novo or it may evolve in a setting of other SM diseases. MCL is very aggressive and usually shows poor response to cytoreduction therapy, such as interferon-alpha, and cladribine. The median survival is only 6 months [1], with rare cases of prolonged survival [3].

D816V of c-KIT is reported in more than 80% of adult SM [4-6] and 46% of MCL [1] and is resistant to imatinib [7]. Studies showed that D816V is sensitive to PKC412 (Commercial name: Midostaurin, Novartis, Switzerland), a novel tyrosine kinase inhibitor, which is undergoing clinical trials for MCL therapy. Here we report one patient with a diagnosis of de novo MCL who had high tumor load at initial presentation. The patient failed cytoreduction therapy. However, she later achieved prolonged survival (101 months at the time of submission) on PKC412/Midostaurin clinical trial. This is the first report of prolonged survival of MCL, well maintained on PKC412/Midostaurin therapy. In addition, the 101-month is the longest survival reported in the literature.

Clinical history

The patient was a 71-year-old woman who initially presented to an outside hospital in September 2005. It was reported that atypical mast cells comprised 60%-70% of marrow cellularity. She did not respond to interleukin-2 or dasatinib therapy at outside hospitals. When she was transferred to Washington University in St. Louis in late 2006, her CBC indices were as follows: white blood cells (WBCs) 5.8 × 10^9/L,

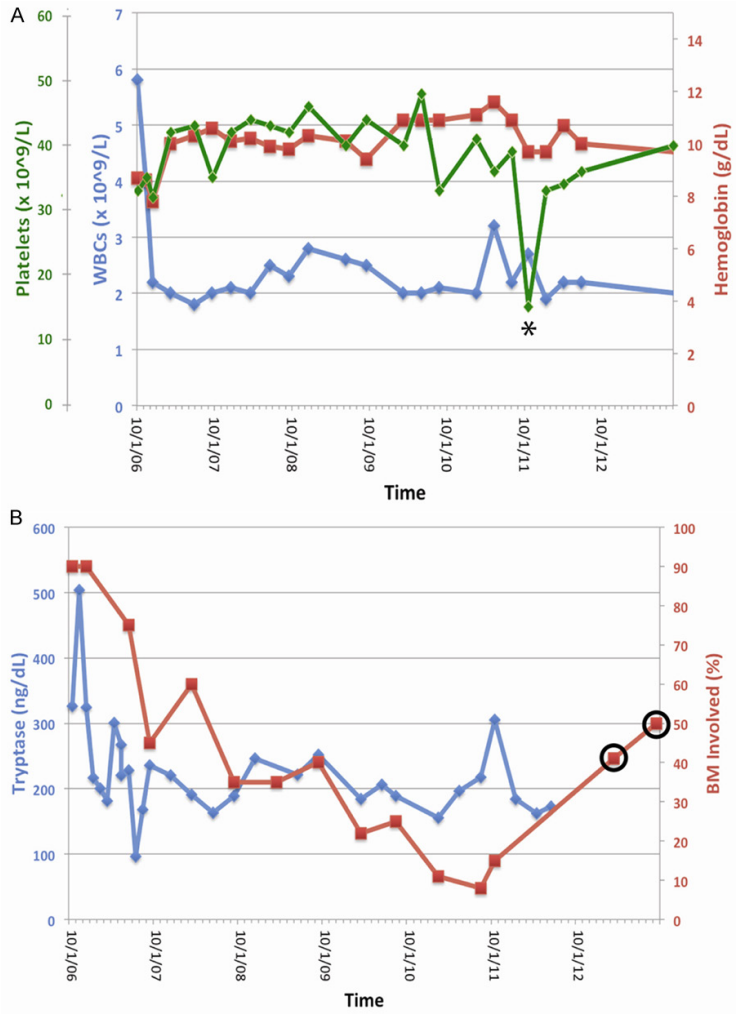

Figure 1. CBC indices, serum tryptase and levels of bone marrow involvement at different time (*x* axle). A: WBCs are usually between 2-3 × 10^9/L; Hgb is generally around 10 g/dL; Platelets are mostly around 30-40 × 10^9/L. Asterisk: platelets were dropped due to unknown reasons in late 2011 and later recovered to the baseline. B: Tryptase is decreased several months after PKC412 therapy and stabilized around 200 ng/mL. Levels of bone marrow involvement are decreased from 90% to below 20% in late 2011. The last two marrow biopsies in 2013 (black circles) show increased involvement, 40%-50%.

hemoglobin (Hgb) 8.7 g/dL, platelets of 32 × 10^9/L. Serum tryptase was markedly elevated to 362 ng/mL. Imaging revealed significant hepatosplenomegaly. A bone marrow biopsy revealed very high tumor load (discussed in *Pathologic Findings*).

The patient was enrolled in a phase II trial of PKC412 (Midostaurin) with daily dose of 100 mg. Her symptoms were gradually improved. After three months on PKC412, her CBC indices were stabilized and she became transfusion independent. Since then she tolerated the therapy well and was stable clinically. Her CBC indices were generally stable at the following levels: WBCs 2 × 10^9/L to 3 × 10^9/L; Hgb 10-11 g/dL, platelets 30 × 10^9/L to 40 × 10^9/L (**Figure 1A**). The tryptase levels decreased to around 200 ng/mL (**Figure 1B**).

Pathologic findings

The initial bone marrow biopsy at our institute revealed a markedly hypercellular bone marrow with approximately 90% atypical mast cells. After enrollment in PKC412 trial, the levels of marrow involvement were gradually decreased to approximately 20% in 2011 (**Figure 1B**). The two most recent bone marrows showed increased levels of marrow involvement by MCL to 40%-50%, which might be due to patchy distribution of neoplastic mast cells, due to the clinical impression of stable disease course.

Multiple follow-up bone marrow biopsies showed similar morphologic features of the neoplastic mast cells. Representative bone marrow biopsies at different time points were shown in **Figure 2**. The neoplastic mast cells formed large clusters and showed bright eosinophilic cytoplasm by chloroacetate esterase stain (**Figure 2A-C**). The neoplastic mast cells were immunoreactive for tryptase (**Figure 2D**), and CD117 (**Figure 2E**). The neoplastic cells were negative for CD2 and CD25 (data not shown). Bone marrow aspirates contained numerous enlarged atypical mast cells, with abundant metachromatic granules (**Figure 2F**). Peripheral blood had never been definitely involved during the whole process, consistent with aleukemic variant of MCL, which is defined as less than 10% circulating mast cells in peripheral blood [2].

The neoplastic mast cells were positive for a D816V mutant of the c-KIT gene. Cytogenetics revealed no detectable abnormalities.

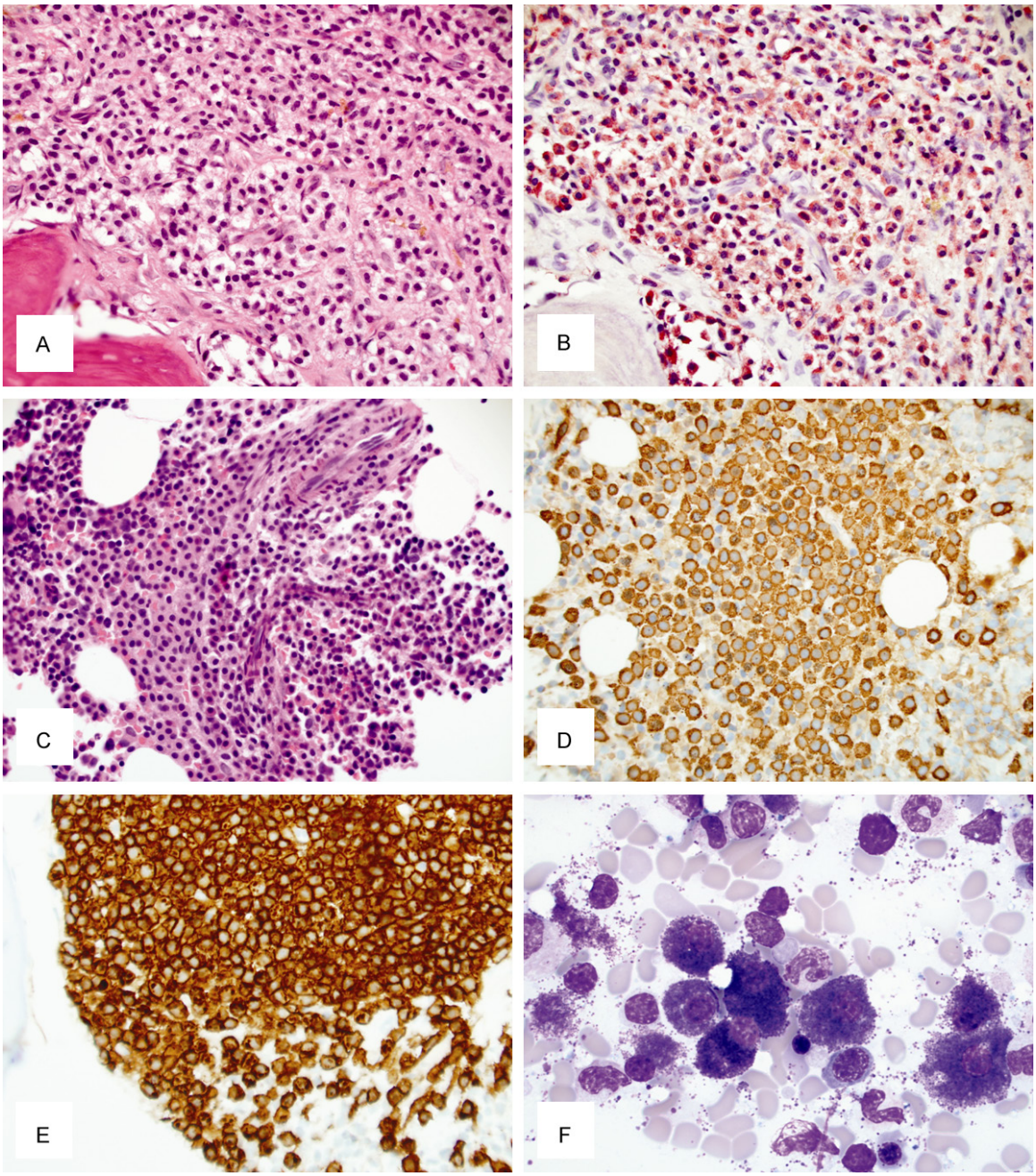

Figure 2. Three bone marrows at different time points. (A, B) The initial bone marrow biopsy at our institute in late 2006. Hematoxylin & Eosin (H & E) stained core biopsy (A) shows increased number of mast cells forming loose clusters. Mast cells are characterized by oval-to-round nuclei, smooth nuclear contours and eosinophilic cytoplasm. The cytoplasm of mast cells shows brightly eosinophilic granules in Chloroacetate Esterase stain (B-E) Bone marrow biopsy in 2010. (H & E) stained core biopsy (C) reveals numerous mast cells forming a tight nodule, which are strongly positive in tryptase (D) and CD117 (E). (F) Bone marrow aspirate in 2013. Wright-Giemsa stain shows many mast cells with metachromatic granules.

Discussion

MCL is a type of aggressive SM and the rarest form of acute leukemia. The patients suffer organ damage and show poor response to cytoreduction therapy with a median survival of 6 months [1].

D816V is a gain-of-function mutation of the activation loop of c-KIT, which is detected in

approximately half of MCL. PKC412 is an N-benzoyl derivative of the alkaloid staurosporine and targets several tyrosine kinases, including D816V. Murine hematopoietic cells over-expressing human D816V mutant are sensitive to PKC412 [8, 9]. In addition, human neoplastic mast cells harboring D816V mutation are sensitive to PKC412 at concentration of 30 nM to 40 nM [9]. The data about the effectiveness of PKC412 in patients are scarce. One MCL patient showed partial response to PKC412 with resolution of liver function abnormalities, decrease of circulating mast cells, and decrease of histamine level [10].

We report a case of de novo aleukemic MCL presenting with high tumor load (approximately 60%-70% of marrow cellularity) at initial diagnosis, which did not respond to either dasatinib or interleukin-2. The patient responded well to 100 mg PKC412 daily, and became transfusion independent after three-month therapy with PKC412. Subsequently her MCL had been stable for the last seven years.

The widely used criteria evaluating therapeutic responses in SM were proposed by Valent *et al* [11]. An important concept of this system is "C-findings", which are clinical evidence of organ damage due to local MC infiltrates. The proposed C-findings include elevated liver function tests and/or ascites, palpable splenomegaly with hypersplenism, bone marrow dysfunction with cytopenias, skeletal lesions and/or fractures, and malabsorption with weight loss due to the gastrointestinal tract involvement. Depending on the extent of C-finding improvement, therapeutic responses are classified into three levels: "major response" (normalization of 1 or more C findings), "partial response" (incomplete improvement of 1 or more C findings), and "progressive disease" (progression of 1 or more C findings, even with improvement of other C-findings). Our patient had two documented C-findings, including bone marrow dysfunction with cytopenias and hypersplenism. Based on Valent's criteria, our patient had achieved a "major response" to PKC412.

It has been suggested that the above-mentioned criteria of SM therapeutic response have several limitations, such as no distinction of the degrees of abnormal laboratory tests; some proposed clinical symptoms are difficult to qualify; no criteria for transfusion-dependent cytopenias; and no requirement of minimal temporal duration of suggested responses. These limitations are not surprising, due to the heterogeneous presentation of SM and limited effects of conventional agents. In order to address these issues and incorporate new knowledge about SM and new therapeutic methods, International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) has proposed a new system of SM therapeutic response [12], which needs time to test its applicability in clinical trials and case studies of SM.

In summary, we report one MCL case which achieved major response to PKC412 and remained stably controlled for the last 7 years. PKC412 helped our patient accomplish a new surviving record of 101 months for MCL. In comparison, the previous longest survival reported is 98 months with an initial tumor load of 30% (Case #8 of Valentini et al.) [3].

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Anjum Hassan, Department of Pathology and Immunology, School of Medicine, Washington University, 660 S. Euclid Ave., Box 8118, St. Louis, MO 63110, USA. Tel: 314-362-1329; Fax: 314-747-4392; E-mail: ahassan@path.wustl.edu

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