Case report

Multiple myeloma presented with tumor fever

Pisa Phiphitaporn[1], Piti Ungarreevittaya[2], Theerin Lanamtieng[1], Chinadol Wanitpongpun[1] and Nattiya Teawtrakul[1]

[1]Division of Hematology, Department of Internal Medicine; [2]Department of Pathology, Faculty of Medicine, Khon Kaen University

Abstract:

Multiple myeloma is a malignant neoplasm of plasma cells that causing prolonged fever due to infectious cause. This is because myeloma cells can suppress normal immunoglobulin production. Rarely, prolonged fever can be caused by the tumor itself. In our multiple myeloma case, the patient presented with prolonged fever despite extensive investigation and negative test results for infection. Fever persisted during antimicrobial treatment and subsided after myeloma treatment. Laboratory tests revealed monoclonal gammopathy and monoclonal plasma cells. After treating with bortezomib, cyclophosphamide and dexamethasone (VCD) regimen, followed by autologous stem cell transplantation, the patient's disease status was in stringent complete remission.

Keywords : ● *Multiple myeloma* ● *Prolonged fever* ● *Tumor fever*

J Hematol Transfus Med. 2023;33:231-6.

Received 30 March 2023 Corrected 1 September 2023 Accepted 1 September 2023

Correspondence should be addressed to Pisa Phiphitaporn M.D., Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen

รายงานผู้ป่วย

ผู้ป่วยมะเร็งไขกระดูกมัยอีโลมาที่มีไข้เรื้อรังจากตัวมะเร็งเอง

พิสาข์ พิพิธพร[1] ปิติ อึ้งอารีย์วิทยา[2] ณัฐติยา เตียวตระกูล[1] ชินดล วานิชพงษ์พันธุ์[1] และ ธีรินทร์ ลาน้ำเที่ยง[1]
[1]อนุสาขาวิชาโลหิตวิทยา [2]อนุสาขาวิชาพยาธิวิทยา สาขาวิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

บทคัดย่อ

มะเร็งไขกระดูกชนิดมัยอีโลมาเป็นมะเร็งที่กำเนิดจากเซลล์พลาสมา โดยปกติหากผู้ป่วยกลุ่มนี้มีภาวะไข้เรื้อรังนั้นมักจะมีสาเหตุมาจากการติดเชื้อซึ่งมีสาเหตุมาจากการสร้างภูมิคุ้มกันที่ผิดปกติไปจากการที่เป็นมะเร็ง พบว่ามีส่วนน้อยมากที่การที่ผู้ป่วยมีภาวะไข้เรื้อรังนั้นมีสาเหตุมาจากตัวโรคมะเร็งมัยอีโลมาเอง รายงานผู้ป่วยฉบับนี้บรรยายถึงผู้ป่วยมะเร็งไขกระดูกมัยอีโลมา ที่มีอาการผิดปกตินำมาโรงพยาบาลคือมีไข้เรื้อรังโดยที่ไม่มีอาการผิดปกติอื่น และตรวจไม่พบการติดเชื้อในระบบใด ร่วมกับผลตรวจเลือดพบภาวะการสร้างภูมิคุ้มกันรูปแบบเดียวและตรวจไขกระดูกพบเซลล์มะเร็งไขกระดูกมัยอีโลมา หลังจากเริ่มการรักษาด้วยยาเคมีบำบัดแบบรับประทาน ร่วมกับยารักษาสมัยใหม่สูตร Bortezomib, Cyclophosphamide and Dexamethasone (VCD) regimenและทำการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดเลือดด้วยเซลล์ของผู้ป่วยเอง พบว่าตัวโรคตอบสนองดีเป็นระยะโรคสงบ

คำสำคัญ : ● *มะเร็งไขกระดูกชนิดมัยอีโลมา* ● *ไข้เรื้อรัง* ● *ไข้จากตัวมะเร็ง*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2566;33:231-6.

Introduction

Multiple myeloma is a malignant lymphoproliferative disorder derived from monoclonal plasma cells. The first mutation leading to initiating plasma cell disorder is in the germinal center during the class switching recombination. Then the tumor cells home to bone marrow via chemokines such as CXCL12, CCR7, CXCR4 then uncontrolled growth leads to increased bone resorption and abnormal secretions of immunoglobulin, which can cause bone fractures, hypercalcemia, immunosuppression, anemia and renal impairment[1-3]. Malignant plasma cells can produce intact immunoglobulin in more than one half of cases (IgG in 50% of cases, IgA in 20% of cases and rarely IgM, IgD, IgE) and free immunoglobulin light chain in 15%[1,4]. Patients with multiple myeloma and prolonged fever rarely present a tumor caused by themselves. Data from the Mayo Clinic indicated 9 patients with multiple myeloma from 5,523 patients that presented fever caused by the multiple myeloma itself[6]. Here, we present a case of an elderly man presenting prolonged fever without organ-specific symptoms. The final diagnosis was multiple myeloma.

Case presentation and clinical course

A 64-year-old man presented low grade fever every day for four months, combined with significant unintentional weight loss of 20 kg within that period. He denied experiencing any organ-specific symptoms, bone pain or palpable masses. Upon physical examination, body temperature 38.5°C and mildly pale conjunctivae were observed, but no jaundice or lymphadenopathy was present. Neither hepatomegaly nor splenomegaly was observed.

He received a diagnosis of multiple myeloma based on the criteria of clonal plasma cells in the bone marrow exceeding 10% and anemia. Following this diagnosis, he was treated with pulse dexamethasone 10 mg intravenous every six hours for four days. Fever subsided after the first dose of dexamethasone then bortezomib, cyclophosphamide and dexamethasone (VCD) regimen was administered and his fever was nonrecurrent. He achieved complete remission after received six cycles of VCD. He then underwent autologous stem cell transplantation and is currently still in a state of stringent complete remission for 25 months.

Table 1 Basic investigation

Complete blood count	
Hemoglobin	10.2 g/dL
White blood cell count	3,890 cell/mm^3
Neutrophil	37.6%
Lymphocyte	45.2%
Monocyte	14.4%
Eosinophil	2.8%
Platelet count	92,000/mm^3
Reticulocyte count	0.2%
Red cell count	4.05 x10^6/uL (4.7-6.2)
Direct antiglobulin test	Positive 2+
Blood chemistry	
BUN	7 mg/dL
Creatinine	0.83 mg/dL
Albumin	3.4 g/dL
Globulin	6.0 g/dL
Total bilirubin	0.4 mg/dL
Direct bilirubin	0.2 mg/dL
ALT	25 U/L
AST	43 U/L
ALP	76 U/L
Beta-2 microglobulin	4.03 mg/L
LDH	120 U/L
Calcium	11.6 mg/dL
Total vitamin	19.6 ng/mL (> 35 ng/mL)
Parathyroid hormone	82.3 pg/mL (15-65 pg/mL)
Infectious profile	
Anti-HIV	Non-reactive
HBsAg	Negative
Anti-HCV	Negative
EBV viral load	Undetectable
CMV viral load	Undetectable
Hemoculture for bacteria	No growth

Table 2 Special investigation

Peripheral blood smear	Normochromic normocytic red cell, no microspherocyte, no polychromasia, white blood cell slightly decreased with lymphocyte predominate, not seen plasma cell, slightly increased monocyte, platelet adequate
Bone marrow aspiration	Normocellularity, M:E 3:1, few maturation arrest of myeloid series, 15-20% young form and bizarre morphology of plasma cell, megakaryocytes are presented in appropriate numbers with normal morphology
Bone marrow biopsy	Cellularity 70%, M:E 6:1, monotypic plasma cell with kappa restriction 15%, megakaryocytes are presented in appropriate numbers with normal morphology
Serum protein electrophoresis (SPEP)	monoclonal gammopathy as Figure 1
Immunofixation	Possible IgG Kappa monoclonal gammopathy
Serum free Kappa/Lambda light chain	157.25/27.6 = 5.7
Immunoglobulin G	3196 mg/dL (700-1600)
Immunoglobulin A	260 mg/dL (70-400)
Immunoglobulin M	52.6 mg/dL (40-230)
Random skin biopsy	Histologic unremarkable skin

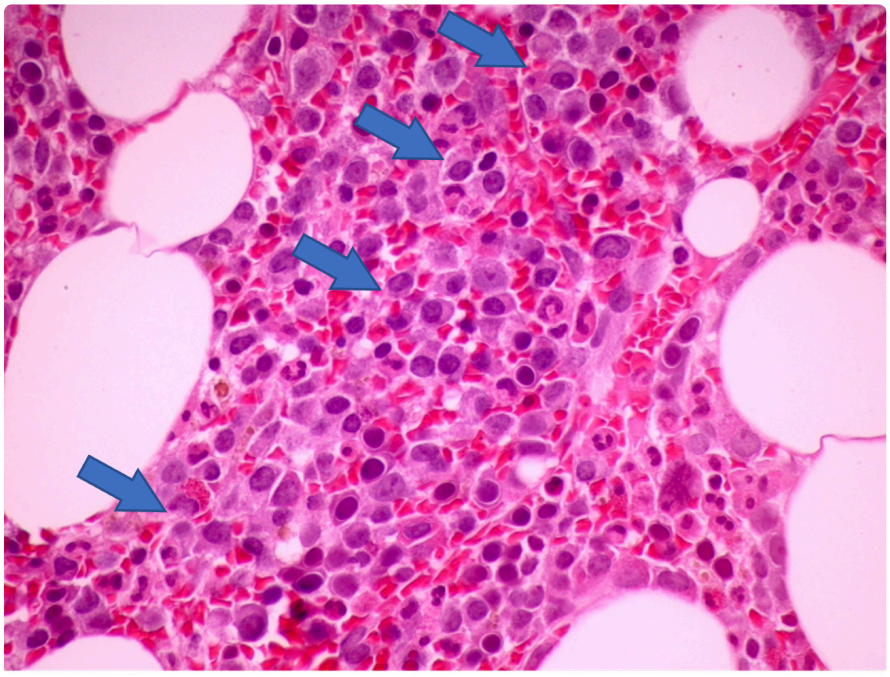

Figure 1 Bone marrow biopsy showing young and bizarre plasma cell 15% of total cells

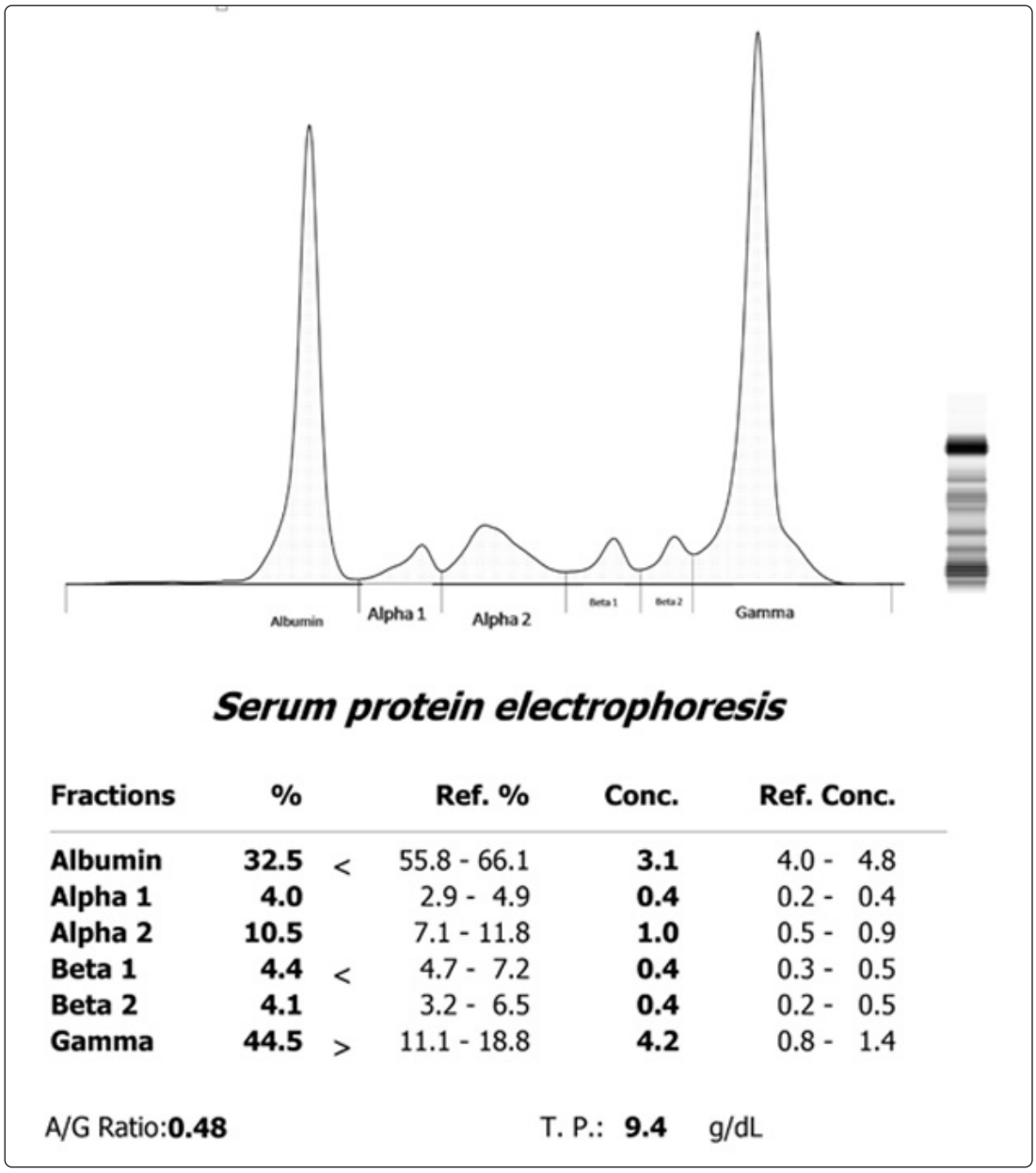

Figure 2 Serum protein electrophoresis (SPEP) shown monoclonal gammopathy at the gamma region

Discussion

Prolonged fever is a common manifestation of many diseases, but not for multiple myeloma, which usually presents with anemia, renal impairment, symptomatic hypercalcemia or pathologic fracture[1,5]. Among patients presenting prolonged fever, the differential diagnosis usually includes low virulent infection, solid organ malignancies, lymphoproliferative disorders (especially lymphoma), and connective tissue diseases. Therefore, among these patients, we investigated according to the clinical of prolonged fever including hemoculture and serology for infections, CT scan and random skin biopsies which were all negative. All of his results led to a diagnosis of multiple myeloma without plasma cell leukemia after extensive review of his monocytes that might be plasma cells in peripheral blood smear. His response to treatment was impressive after one cycle of induction treatment with VCD regimen[6].

Among patients receiving a diagnosis of multiple myeloma who also present fever, an infectious cause should be considered due to the monoclonal plasma cells being impaired in their ability to fight off infec-

tions. Administration of myeloma treatment, including chemotherapy and steroids, could worsen the condition if an infectious cause is not ruled out. If an infectious cause is excluded, there may be neoplastic processes causing tumor fever due to the increased levels of inflammatory cytokines such as IL-6, IL-1β, and TNF-β in multiple myeloma[7,8]. However, questions remain to discover why our case did not have much tumor burden defined by degree of anemia, serum free light chain and percent of monoclonal plasma cells in bone marrow while many patients have advanced disease but without presenting tumor fever.

From this case we suggest that among patients presenting prolonged fever without specific organ symptoms and laboratory results showing hypergammaglobulinemia that can be polyclonal or monoclonal gammopathy should test for serum protein electrophoresis (SPEP). SPEP is useful and cost effective. When patients present monoclonal gammopathy they should be further investigated for lymphoproliferative disorder such as lymphoma or multiple myeloma. On the other hand when patients have polyclonal gammopathy they should be looking for infectious causes or autoimmune disorders.

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