American Journal of Hematology 64:76–77 (2000)

Multiple Myeloma Presenting High Fever and High Serum Levels of Lactic Dehydrogenase, CRP, and Interleukin-6

Hirokazu Murakami,[1]* Satoru Takada,[2] Nahoko Hatsumi,[2] Akihiko Yokohama,[3] Takayuki Saitoh,[2] Hideki Uchiumi,[2] Tadashi Maehara,[2] Takafumi Matsushima,[2] Norifumi Tsukamoto,[2] Kimio Morita,[1] Jun'ichi Tamura,[2] Morio Sawamura,[4] and Masamitsu Karasawa[3]

[1]School of Health Sciences, Faculty of Medicine, Gunma University, Maebashi Gunma, Japan
[2]Third Department of Internal Medicine, Gunma University School of Medicine, Maebashi, Gunma, Japan
[3]Division of Blood Transfusion Service, Gunma University Hospital, Maebashi, Gunma, Japan
[4]Division of Internal Medicine, Nishigunma Hospital, Shibukawa, Gunma, Japan

Two myeloma patients presented high fever with no signs or data indicating infection at diagnosis or relapse. Both patients had plasmablastic myeloma, and serum levels of lactic dehydrogenase (LDH) and CRP were extremely high. Plasmablastic morphology, high LDH, and CRP were recognized as poor prognostic factors, indicating a fulminant phase of multiple myeloma. Interleukin-6 (IL-6) was only high in measured cytokines. We proposed that IL-6 caused high fever and induced the fulminant phase in these 2 cases. Am. J. Hematol. 64:76–77, 2000. © 2000 Wiley-Liss, Inc.

Key words: myeloma; fever; IL-6; LDH; CRP

Multiple myeloma (MM) is the major malignancy of plasma cells comprising approximately 10% of hematological malignancies [1]. Osteolytic lesions in bones or diffuse osteoporosis with or without fractures, anemia, and hyperviscosity syndrome are the most common features, however high fever is a rare complication except in patients with infections.

We report here 2 patients presenting high fever and high serum levels of lactic dehydrogenase (LDH), CRP and interleukin-6 (IL-6).

CASE REPORT

Case 1

A 48-year-old male was admitted to our hospital in April 1995 because of a high fever and back pain and was was diagnosed as having MM (Bence Jones, κ type, stage III A). No signs or data indicated infection. He was treated with intermittent melphalan-prednisolone (MP) therapy, and achieved a partial response. High fever discontinued after the first course of MP therapy. He received 10 additional courses of MP therapy as an outpatient. The disease relapsed with a high fever and anemia in March 1996, and the patient was re-admitted on March 30, 1996. No signs or data indicated infection. The blood counts were hemoglobin (Hb) 6.6 g/dL, platelet count (Plt) $35.5 \times 10^4/\mu L$, and white blood cell count (WBC) 12,900/μL with 11.5% of myeloma cells. Over 20% of abnormal large plasma cells were seen in a bone marrow specimen. Bence Jones protein was 2.16 g/day. The levels of serum total protein, LDH, Ca, β-2-microglobulin, CRP, and IL-6 were 6.6 g/dL (6.3–7.9), 525 IU/L (230–420), 12.2 mg/dL (8.9–10.1), 4.22 mg/dL (0.6–2.0), 27.5 mg/dL (<0.1), and 404 pg/mL (<4.0), respectively. Serum interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) were not detected. After 1 course of VAD therapy, the fever diminished and the serum levels of LDH and CRP recovered. Serum IL-6 was not detected 21 days after chemotherapy. His disease re-relapsed on

*Correspondence to: Hirokazu Murakami, School of Health Sciences, Faculty of Medicine, Gunma University, Maebashi Gunma 371-8514, Japan.

Received for publication 29 October 1999; Accepted 1 December 1999

the 41st hospital day, and became refractory to further therapy. Serum IL-6 level elevated to 325 pg/mL. He died on the 47th hospital day.

Case 2

A 45-year-old male was admitted to our hospital in September 1995 because of back pain. He was diagnosed as having MM (IgG, κ type, stage III A). He was treated with 7 courses of MCNU-VMP therapy, and achieved complete response. After 6 courses of additional MP therapy as an outpatient, the disease relapsed with a high fever, and he was re-admitted on September 17, 1996. No signs or data indicated infection. The blood counts were Hb 10.7 g/dL, Plt $4.5 \times 10^4/\mu L$, and WBC 2,700/μL. 16.6% of abnormal plasma cells were seen in a bone marrow. The levels of serum total protein, LDH, Ca, B2 microglobulin, CRP, and IL-6 were 9.2 g/dL, 2696 IU/L, 8.6 mg/dL, 7.2 mg/dL, 3.4 mg/dL, and 12.3 pg/mL, respectively. Serum IL-1β and TNF-α were not detected. His disease was refractory to chemotherapy, and the level of serum IL-6 was continuously high. He died on 67th hospital day.

DISCUSSION

We described 2 myeloma patients presenting high fever, which is a rare complication in this disease. High serum levels of lactic dehydrogenase, CRP and interleukin-6 were observed in these 2 patients. MM is a clonal B cell malignancy that affects plasma cells and is recognized to proceed through different phases: an inactive phase in which tumor cells are nonproliferating mature plasma cells, an active phase with a small percentage of proliferating plasmablastic cells, and a fulminant phase with increased plasmablastic cells [2]. The first case showed the fulminant phase at diagnosis, and the second case relapsed as fulminant myeloma. Daeninck et al. reported a myeloma patient clinically presenting lymphoma, who complained of fever and lymphadenopathy [3]. In this patient, serum LDH and CRP levels were elevated. Barlogie B et al. reported that high levels of serum LDH indicated high-grade lymphoma-like myeloma [4].

CRP is an acute-phase protein whose production is controlled by IL-6 [5], and is recognized as a poor prognostic factor in multiple myeloma [6].

IL-6, a pleiotropic cytokine produced by various cells, plays a central role in both host defense mechanisms and acute-phase responses. Many studies agreed that large amounts of IL-6 are produced by the tumoral microenvironment in response to stimulating myeloma cells [7,8]. Our 2 patients complained of high fever; however, no signs or data indicated infection. The serum IL-6 level was only elevated in measured cytokines. We proposed that IL-6, produced by the microenvironment, caused a high fever and high serum levels of CRP, and induced the fulminant phase in these 2 cases.

REFERENCES

1. Kyle R. Multiple myeloma: a review of 869 cases. Mayo Clin Proc 1975;50:29–40.
2. Hallek M, Bergsagel PL, Anderson KC. Multiple myeloma: Increasing evidence for a multistep transformation process. Blood 1998;91:3–21.
3. Daeninck PJ, Williams GJ, Rubinger M, Johnston JB. Multiple myeloma presenting clinically as lymphoma. Leuk Lymph 1997;28:195–201.
4. Barlogie B, Smallwood L, Smith T, Alexanian R. High serum levels of lactic dehydrogenase identify a high-grade lymphoma-like myeloma. Ann Int Med 1989;110:521–525.
5. Castell JV, Gomez-Lechon MJ, David M, Fabra R, Trullenque R, Heinrich PC. Acute phase response of human hepatocytes: Regulation of acute phase protein synthesis by interleukin-6. Hepatology 1990; 12:1179–1186.
6. Bataille R, Boccadoro M, Klein B, Pileri A. C-reactive protein and β 2-microglobulin produces a simple and powerful myeloma staging system. Blood 1992;80:733–737.
7. Klein B, Zhang XG, Jourdan M, Content J, Houssiau F, Aarden L, Piechaczyk M, Bataille R. A paracrine rather than autocrine regulation of myeloma cell growth and differentiation by interleukin-6. Blood 1989;73:517–526.
8. Portier M, Razjbaum G, Xhang XG, Attal M, Rusalen C, Wijdenes J, Mannoni P, Piechaczyk M, Bataille R, Klein B. In vitro interleukin-6 gene expression in the tumoral environment in multiple myeloma. Eur J Immunol 1991;21:1759–1762.