Cytokines in Inflammatory Malignant Fibrous Histiocytoma Presenting With Leukemoid Reaction

By Mona F. Melhem, Arnold I. Meisler, Reisuke Saito, Gene G. Finley, Helen R. Hockman, and Raymond A. Koski

Inflammatory malignant fibrous histiocytomas (IMFH) are rare tumors and are frequently associated with leukocytosis. In rare cases, leukemoid reactions were attributed to tumor production of unidentified hematopoietic factors. In this study, we used immunohistochemical techniques to show cytokine immunoreactivity in the malignant cells of two cases of IMFH presenting with leukemoid reactions and compared them with two malignant fibrous histiocytomas, noninflammatory type. All four tumors stained positively for stem cell factor (SCF), granulocyte colony-stimulating factor (G-CSF), interleukin-2 (IL-2), IL-4, IL-5, interferon-α (IFN-α), and insulin-like growth factor-I. Other cytokines detected only in the two IMFH included IL-6, IL-7, IL-8, IFN-γ, and keratinocyte growth factor. Granulocyte-macrophage-CSF, IL-3, and transforming growth factor-β staining was present in one of the two IMFH tumors and was not present in the noninflammatory tumors. The immunohistochemical staining was localized to the malignant cells, suggesting deregulated cytokine expression consistent with their monocytic/histiocytic origin. Expression of certain cytokines in the IMFH may account for the local inflammatory infiltrate, tumor fibrosis, and the aggressive nature of the malignant cells. We also detected elevated serum levels of SCF, G-CSF, IL-6, and tumor necrosis factor in one or both of the IMFH patients. These latter observations may explain the bone marrow hypercellularity and other paraneoplastic symptoms, including fever, malaise, and weight loss, observed in both patients. Different cytokines present in the two IMFH tumors appear to be responsible for the eosinophilic leukemoid reaction observed in one case and for the granulocytic leukemoid reaction observed in the other patient. They may also be responsible for expansion of the tumor-cell population, fibroblast proliferation, and enhanced secretion of extracellular collagen.

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MATERIALS AND METHODS

Patients

Patient 1. A 63-year-old black man presented with a 1-year history of enlarging abdominal mass and weight loss. A computed tomography (CT) scan showed an 11 × 22 cm retroperitoneal mass...
extending from the level of L3 vertebra into the posterior mediastinum. An attempt at resecting the tumor resulted in 5% to 10% residual mass left because of the extensive involvement around major blood vessels. This was followed by radiation therapy. The patient was readmitted 1 year later with fever, abdominal pain, and a fivefold increase in the residual mass shown on CT scan. A blood count showed anemia and leukocytosis (58 × 10^9/L) with the following differential: 35% neutrophils (20.3 × 10^9/L), 36% band neutrophils (20.88 × 10^9/L), 26% eosinophils (15.08 × 10^9/L), 1% monocytes (0.58 × 10^9/L), and 2% lymphocytes (1.16 × 10^9/L). A leukocyte alkaline phosphatase score (LAP) of 210 was consistent with a leukemoid reaction. A BM biopsy showed a hypercellular marrow with myeloid predominance, neutrophilia, and eosinophilia. No evidence of tumor metastasis was seen. Cytogenetic analysis of BM aspirate showed no structural chromosomal anomaly. The patient died 16 months after original diagnosis with a WBC count reaching 164 × 10^9/L and severe leftward shift. His WBC differential at this point was 6% neutrophils (9.84 × 10^9/L), 46% band neutrophils (75.44 × 10^9/L), 1% lymphocytes (1.64 × 10^9/L), 1% monocytes (1.64 × 10^9/L), 24% eosinophils (39.36 × 10^9/L), 10% metamyelocytes (16.4 × 10^9/L), 6% myelocytes (9.84 × 10^9/L), 5% promyelocytes (8.2 × 10^9/L), and 1% blasts (1.64 × 10^9/L).

Patient 2. A 67-year-old Caucasian man presented with 1-month history of fatigue, anorexia, and 10 kg weight loss. On presentation, physical exam showed a palpable, smooth, nontender liver. The blood count showed a leukocytosis (62 × 10^9/L) with the following differential: 53% neutrophils (32.86 × 10^9/L), 41% band neutrophils (25.42 × 10^9/L), 1% lymphocytes (0.62 × 10^9/L), 3% monocytes (1.86 × 10^9/L), 1% myelocytes (9.84 × 10^9/L), and 1% basophils (0.62 × 10^9/L). The LAP score of 378 was consistent with a leukemoid reaction. A BM biopsy showed a hypercellular marrow with myeloid predominance, neutrophilia, and eosinophilia. No evidence of tumor metastasis was seen. Cytogenetic analysis of BM aspirate showed no structural chromosomal anomaly. A CT scan showed a large retroperitoneal right-sided mass involving the right kidney. A biopsy of the mass was diagnosed as IMFH. The patient deteriorated clinically, necessitating an emergency laparotomy that showed widespread metastatic tumor involving the omentum and liver. The patient died 2 weeks after diagnosis. His WBC count had reached 156 × 10^9/L with the following differential: 28% neutrophils (43.68 × 10^9/L), 68% band neutrophils (106.08 × 10^9/L), 2% metamyelocytes (3.12 × 10^9/L), 1% lymphocytes (1.56 × 10^9/L), and 1% monocytes (1.56 × 10^9/L). A summary of the clinical data and the differential blood count is presented in Table 1.

Control patients were 56- and 72-year-old men presenting with IMFH. Portions of the IMFH tumors and of the control tumors (malignant fibrous histiocytomas, noninflammatory type) were fixed in 10% buffered formalin and processed for paraffin embedding. Five-micron sections of each tumor were deparaffinized, rehydrated, and stained with hematoxylin and eosin for routine histologic evaluation. Special stains were performed to confirm the histologic diagnosis of the tumors and included immunoperoxidase staining for alpha-1-antitrypsin (AAT), carcinoembryonic antigen, prekeratin, epithelial membrane antigen, desmin, S-100, leukocyte common antigen (LCA), and Leu-M1 (Becton Dickinson Immunohistochemistry Systems, San Jose, CA). Antibodies were used at dilutions recommended by the manufacturer. Indirect immunoperoxidase staining used the avidin-biotin complex method (Vectastain Elite ABC kits; Vector Laboratories, Burlingame, CA) with 3,3-

### Table 1. Clinical Summary and Peripheral Blood Data

<table>
<thead>
<tr>
<th>WBC Count [10^9/L]</th>
<th>Neutrophils (%)</th>
<th>Band Neutrophils (%)</th>
<th>Eosinophils (%)</th>
<th>Lymphocytes (%)</th>
<th>Monocytes (%)</th>
<th>LAP Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>156</td>
<td>43.68</td>
<td>106.08</td>
<td>3.12</td>
<td>1.56</td>
<td>1.56</td>
<td>378</td>
</tr>
</tbody>
</table>

- LAP: Leukocyte alkaline phosphatase.
- Normal range for LAP score: 10 to 50.

Histologic and Immunohistochemical Studies of the Tumors

Portions of the IMFH tumors and of the control tumors (malignant fibrous histiocytomas, noninflammatory type) were fixed in 10% buffered formalin and processed for paraffin embedding. Five-micron sections of each tumor were deparaffinized, rehydrated, and stained with hematoxylin and eosin for routine histologic evaluation. Special stains were performed to confirm the histologic diagnosis of the tumors and included immunoperoxidase staining for alpha-1-antitrypsin (AAT), carcinoembryonic antigen, prekeratin, epithelial membrane antigen, desmin, S-100, leukocyte common antigen (LCA), and Leu-M1 (Becton Dickinson Immunohistochemistry Systems, San Jose, CA). Antibodies were used at dilutions recommended by the manufacturer. Indirect immunoperoxidase staining used the avidin-biotin complex method (Vectastain Elite ABC kits; Vector Laboratories, Burlingame, CA) with 3,3-
dilutions of 1:200 to 1:1,000. Endogenous peroxidase was blocked with 0.3% H2O2.

In addition to the routine diagnostic immunohistochemical studies listed above, a panel of polyclonal rabbit antibodies raised against recombinant human cytokines and growth factors were used to stain tumor sections. Rabbit antisera recognizing G-CSF, GM-CSF, IL-1β, IL-2, IL-3, IL-4, IL-5, IFN-α-Con1, IFN-γ, acidic fibroblast growth factor (FGF), TNF, keratinocyte growth factor (KGF), insulin-like growth factor-1 (IGF-I), transforming growth factor-β (TGF-β) (provided by H. Hockman, Amgen Inc, Thousand Oaks, CA), TGF-α (provided by Margery Nicolson; Amgen, Inc), and SCF (obtained from Joan Egrie, Amgen, Inc) were used at dilutions of 1:200 to 1:1,000. Negative controls for these antisera included preimmune sera from the corresponding rabbits. Protein A-purified rabbit anti-PDGF-BB antibody (from Julia Tseng, Amgen, Inc) was used at 6 μg/mL. Rabbit anti-basic FGF and anti-IL-6 antibodies were affinity-purified against the immunizing cytokine and used at 3 to 9 μg/mL concentrations. These affinity-purified antibodies were provided by Michael Fox (Amgen, Inc), and Larry Bennett (Amgen Boulder, Inc, Boulder, CO), respectively. Rabbit anti-IL-7 antibody affinity-purified against IL-7 and rabbit anti-IL-8 antibody affinity-purified against IL-8 were purchased from Biosource International (Camarillo, CA) and used at 5 μg/mL.

Histologic Examination of BM Biopsy Specimens

Core BM biopsy specimens were obtained from the superior posterior iliac fossa. The biopsy specimens were fixed in Zenker’s fixative, decalcified, and processed for paraffin embedding. Five-micron sections were stained with hematoxylin and eosin and examined microscopically.

Serum Assays

IL-1β serum levels were determined using an enzyme-linked immunosorbent assay (ELISA) kit from Cistron Biotechnology (Pine Brook, NJ). G-CSF, IL-4, and IL-6 levels were determined with enzyme immunoassays (Quantikine kits; R&D Systems, Minneapolis, MN). IFN-γ and GM-CSF levels were determined using ELISA kits from Endogen Inc (Boston, MA). IL-2 and TNF were determined using an immunoradiometric assay kit purchased from Medgenix (Brussels, Belgium). All kits were used according to the manufacturer’s directions. Serum SCF levels were measured by enzyme immunoassays as described by Langley et al.12

RESULTS

Histologic examination of all four tumors showed partially encapsulated growth. The large polygonal tumor cells had pleomorphic nuclei, prominent nucleoli with atypical mitoses, abundant cytoplasm, and were embedded in thick fibrous stroma. Numerous acute inflammatory cells, mainly polymorphonuclear leukocytes, were seen infiltrating two of the tumors that were accompanied with the leukemoid reaction, without evidence of cell necrosis. Prominent leukaphagocytosis was seen (Fig 1A and B). These tumors were classified as malignant fibrous histiocytoma, inflammatory type, whereas the other two were diagnosed as malignant fibrous histiocytoma, noninflammatory type. The malignant and xanthoma cells stained positive with AAT, as expected, whereas the background inflammatory infiltrate in IMFH was positive with LCA. The tumors were negative with all of the other antibodies used for differential diagnosis. Histologic examination of BM biopsy specimens from both IMFH patients showed hypercellular marrow with myeloid predominance (Fig 1C). The control noninflammatory malignant fibrous histiocytoma tumors consist of large irregular cells with irregular and atypical nuclei, imbedded in a thick fibrous stroma without evidence of inflammatory cell infiltrate (Fig 1D).

The results of immunohistochemical staining with anticytokine antibodies are presented in Table 2. In both IMFH, malignant cells showed consistent positivity for G-CSF, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, SCF, IFN-α, IFN-γ, KGF, and IGFl. Interestingly, the second tumor showed a much higher concentration of IL-6 as determined by a higher intensity of staining. Examples of the immunohistochemical reactions showing cytokine localization within the malignant histiocytes are presented in Fig 2.

The control noninflammatory malignant fibrous histiocytoma tumors were consistently positive for SCF, G-CSF, IL-2, IL-4, IL-5, IFN-α, and IGFl. In contrast to the 2 inflammatory tumors, the noninflammatory tumors were specifically negative for IL-6, IL-7, IL-8, IFN-γ, and KGF.

Serum Cytokine Assays

Enzyme immunoassays of IMFH patients' sera detected elevated levels of SCF, IL-6, G-CSF, and TNF (Table 3). SCF serum levels were above mean normal levels in patient

Fig 1. (A) Inflammatory malignant fibrous histiocytoma tumor resected from patient no. 1. Note the large pleomorphic malignant cells showing leukaphagocytosis (large arrow) and the heavy acute inflammatory infiltrate (small arrows) in a dense fibrous stroma. (Hematoxylin and eosin [H&E], original magnification X 400.) (B) High power view of the tumor from patient no. 2 showing an atypical mitotic figure of the malignant histiocyte (arrow). Also note the heavy acute inflammatory infiltrate (small arrows). (H&E, original magnification X 400.) (C) BM biopsy specimen from patient no. 1 showing hypercellular marrow loaded with a large number of mature and immature eosinophils (arrows). (H&E, original magnification X 600.) (D) Malignant fibrous histiocytoma, noninflammatory type. Note the large pleomorphic malignant cells similar to those seen in (A), arrow, and the lack of inflammatory infiltrate. (H&E, original magnification X 400.)

Fig 2. Examples of immunohistochemical staining of tumor with (A) G-CSF (B) IL-3, (C) SCF and (D) IL-8. Note the localization of the positive staining within the large malignant cells (arrows). (E) Nonspecific isotype negative control. Original magnifications: (A) and (C), X 100; and (B), (D), and (E), X 400.
DISCUSSION

IMFH is a peculiar and rare soft tissue tumor that resembles benign xanthogranuloma. The main malignant cell in these tumors is a primitive histiocyte/macrophage, capable of mitotic division and phagocytosis. The heavy inflammatory infiltrate within the tumor suggests the presence of either chemotactic factors and/or hematopoietic growth factors within these tumors. These may be produced by the malignant histiocytes and show a local effect on hematopoietic cells. To date, there is no evidence of an autocrine or paracrine growth factor pathway for this tumor that involves any of the cytokines observed. This may be because of the rarity of these tumors and the lack of fresh or frozen tissues suitable for studying the status of the receptors for each cytokine detected.

The clinical presentation, including fever, malaise, and leukocytosis, suggested an infection, but exhaustive microbiologic workup did not yield any microorganisms. BM biopsy specimens, when biopsies were performed, showed myeloid hyperplasia. The occurrence of peripheral blood leukocytosis and rare leukemoid reactions suggested a systemic effect of growth factors produced by these tumor cells.

The possibility of IMFH tumor cells producing a hematopoietic growth factor was raised by Roques et al in 1979 but has not been confirmed to date. In this study, we show positive tumor cell immunoreactivity for a number of hematopoietic growth factors in two IMFH tumors associated with a leukemoid reaction. Cytokine production by these tumor cells is consistent with their histiocytic/monocytic origin. Monocytes produce a variety of cytokines, as reviewed by Ziegler-Heitbrock and Nathan. Deregulated expression of cytokines in malignant cells of IMFH can account for many of the clinical symptoms, including local inflammatory infiltrate, BM hyperplasia, leukocytosis or leukemoid reaction, fibrotic reaction, and the aggressive nature of the tumor cells. In several published cases, the production of cytokines by IMFH tumor cells is supported by the fact that the peripheral WBC counts returned to normal after resection of the tumor but increased again to preresection levels as the tumors recurred and progressed. Unfortunately, we could not observe the latter in our two patients because of the advanced stages of the disease and unresectability of the tumors.

Cytokines detected immunohistochemically in fibrous histiocytoma tumor cells (Table 2) may contribute to the maintenance and proliferation of the malignant histiocytes and the pathogenesis of these tumors. For example, IFN-γ, IL-3, GM-CSF, and G-CSF in combination were shown to activate monocytes in the acute response to infection. IL-2 enhances the proliferation of monocytes and their cytotoxic activity, and IL-4 induces monocyte differentiation and phagocytosis. The latter two ILs were detected in all four tumors and may contribute to the histogenesis of the malignant cells in these neoplasms as well as to their abundant leukohagocytic activity. IL-2 also induces neutrophilia and eosinophilia in humans and induces M-CSF, GM-CSF, IL-3, and IL-5 expression in human peripheral blood mononuclear cells (PBMC).

In this study, IL-6, IL-7, IL-8, IFN-γ, and KGF were detected in the two inflammatory tumors presenting with leukemoid reaction, and not in the noninflammatory histiocytomas. IL-7 is known to enhance the proliferation and differentiation of B and T lymphocytes. It also induces leukocytosis in mice and secretion of IL-1, TNF, and IL-6 from human PBMC. Through its stimulation of IL-1 production, also known as fibroblast activating factor, it may be partially responsible for the fibroblastic differentiation of these tumors.

IL-8, also known as monocye-derived neutrophil chemotactic factor, is a strong neutrophil chemotactic and activating cytokine. It also caused neutrophilia in rabbits in vivo. It was detected in the inflammatory tumors and not in the noninflammatory tumors. IL-8 induction of the dense neutrophilic infiltrates and hence may be one of the most important features of the IMFH tumors.

SCF is an early acting hematopoietic growth factor that stimulates the proliferation of BM stem cells and has a wide range of activity on myeloid, lymphoid, and erythroid cell progenitors. It synergizes with other factors to cause proliferation and differentiation of committed progenitor cells. SCF increases the number of peripheral blood erythrocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils, and increases BM cellularity in baboons. The coinjection of SCF and G-CSF increased BM neutrophils and caused peripheral neutrophilia in rats. Its presence in IMFH and noninflammatory malignant fibrous histiocytomas may contribute to the proliferation of the malignant histiocytes/macrophages and, therefore, may be responsible for the aggressive nature of these tumors.

Different combinations of cytokines produced from each tumor might explain the presence of the leukemoid reaction with certain tumors and not others, as well as the different cell types in the leukemoid reactions seen in the two patients. Whereas GM-CSF and IL-3 increase the number of eosinophil colony-forming units (CFU-Eo), IL-5 acts on the later stages of eosinophil maturations. Tumor cell production of these three cytokines may explain the eosinophilic-leukemoid reaction and BM eosinophilia in patient no. 1 that was not present in the other patients.

The elevated serum IL-6 levels in patient no. 1 may be attributed to IL-6 secretion by the circulating eosinophils. IL-6 directly supports neutrophil/macrophage colonies and, through accessory cells, stimulates the production of several different types of colonies from normal murine BM. This, together with the expression of many other cytokines, particularly IL-3 and IL-5, by the tumor cells in patient no. 1, may contribute to the absolute neutrophilia together with eosinophilia in the peripheral blood. The higher than normal serum SCF and G-CSF levels in patient no. 2 (Table 3) can explain the etiology of the mainly neutrophilic-leukemoid reaction and BM neutrophilia in this patient. Rats injected
daily with SCF and G-CSF for 1 week resembled patient no. 2 in several aspects, including neutrophilia (>60 × 10⁹ PMN/L), an increase in circulating immature myeloid cells, and myeloid hyperplasia and neutrophilia in the BM.²⁷

Whereas IFN-α occasionally inhibits tumor growth, it stimulates macrophages and also may contribute to the leukophagocytosis seen in this specific type of malignancy. IFN-α is also known to cause fever, chills, and anorexia, ie, symptoms usually found in IMFH patients. These symptoms, also known as paraneoplastic syndromes, are generally attributed to the systemic effects of malignant growth. They can now be explained in these patients by the production of IFN-α by tumor cells and its release into the circulation. IFN-γ, despite its antiproliferative activity on tumor cells in vitro, activates macrophages, and its presence in IMFH may explain the leukophagocytosis of the malignant macrophages in these tumors. IGF-I stimulates macrophage growth and fibroblast growth. TGF-β was detected in the second tumor. It stimulates proliferation of fibroblasts and enhances secretion of the extracellular matrix, including collagen. Expression of IGF-I and TGF-β by IMFH tumor cells could account for the thick fibrous stroma found in the tumors. TGF-β also stimulates human PBMC chemotaxis and IL-1 expression in PBMC. IGF-I, but not TGF-β, was detected in the two noninflammatory fibrous histiocytomas.

Cytokine immunoassays provide insight into some of the clinical changes attributed to human cancers. Tumor cells stain positive immunohistochemically for factors with potential autocrine, paracrine, and chemotactic activities. Circulating factors detected by serum assays can explain paraneoplastic syndromes such as leukocytosis. However, it is important to consider the limitations of these assays. Intense intracellular staining may result from increased synthesis of a factor or from low levels of synthesis accompanied by inefficient secretion. Elevated serum levels of a growth factor with low-intensity immunohistochemical tumor staining could result from high secretion rates or simply from distant synthesis of the cytokine. For example, TNF was not detected within IMFH tumor cells by immunohistochemical staining, but was present at high levels in the patients' sera. Serum assays also may not detect tumor cell cytokine production, particularly when the factor is rapidly eliminated from circulation or is bound to serum constituents that interfere with the assays. A more complete description of growth factors and cytokines contributing to leukemoid reactions and other paraneoplastic syndromes awaits systematic studies and serum assays with enhanced sensitivities.

### Table 2. Immunohistochemical Staining of Tumors for Cytokines and Growth Factors

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Tumor 1</th>
<th>Tumor 2</th>
<th>Control 1</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCF</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>G-CSF</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IL-1β</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IL-2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>IL-3</td>
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<td>IFN-α</td>
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<td>-</td>
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<td>TGF-α</td>
<td>-</td>
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<td>TGF-β</td>
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<td>PDGF-BB</td>
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<td>KGF</td>
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<tr>
<td>IGF-I</td>
<td>+</td>
<td>++</td>
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</tbody>
</table>

Table 2: Tumors considered positive had immunohistochemical staining of the malignant cells with essentially negative background. Staining intensity was graded on a scale of 0 (−) to ++. * Control 1 and control 2 are two cases of malignant fibrous histiocytomas, noninflammatory type.

### Table 3. Serum Cytokine Assays

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Patient No. 1</th>
<th>Patient No. 2</th>
<th>Normal Value</th>
<th>Test Sensitivity</th>
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</thead>
<tbody>
<tr>
<td>SCF</td>
<td>4,070</td>
<td>5,120</td>
<td>3,310 ± 1,090</td>
<td>500</td>
</tr>
<tr>
<td>G-CSF</td>
<td>ND</td>
<td>590</td>
<td>&lt;77</td>
<td>11</td>
</tr>
<tr>
<td>GM-CSF</td>
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<td>ND</td>
<td>&lt;10</td>
<td>5</td>
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<tr>
<td>IL-1</td>
<td>ND</td>
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<td>ND</td>
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<td>IL-2</td>
<td>ND</td>
<td>ND</td>
<td>&lt;4</td>
<td>1</td>
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<td>IL-4</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>4.1</td>
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<tr>
<td>IL-6</td>
<td>34</td>
<td>18</td>
<td>&lt;3</td>
<td>0.35</td>
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<tr>
<td>IFN-γ</td>
<td>ND</td>
<td>ND</td>
<td>&lt;10</td>
<td>5</td>
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<tr>
<td>TNF</td>
<td>16</td>
<td>12</td>
<td>6.3</td>
<td>5</td>
</tr>
</tbody>
</table>

All the values are in picograms per milliliter.

Abbreviations: ND, not detected; NA, not available.

### ACKNOWLEDGMENT

We thank Amgen, Inc for recombinant cytokines; Joan Eegre, Margery Nicolson, Larry Bennett, Michael Fox, and Julia Tseng for anti-cytokine antibodies; Sue Yancik, Jim Klenner, and Judy Cribbs for performing serum cytokine assays; and E. Sonmez-Alpan for technical assistance.

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