JOP. J Pancreas (Online) 2006; 7(6):631-634.

CASE REPORT

Leukemoid Reaction in Pancreatic Cancer: A Case Report and Review of the Literature

Khusroo M Qureshi[1], Arun K Raman[2], Dongfeng Tan[1], Marwan G Fakih[1,2]

[1]Department of Medicine, Roswell Park Cancer Institute; [2]Department of Medicine, University at Buffalo School of Medicine and Biomedical Sciences. Buffalo, NY, USA

ABSTRACT

Context The presentation of pancreatic cancer with a leukemoid reaction is rare with no prior reports in the English language literature.

Case report We report a case of advanced pancreatic cancer presenting with leukemoid reaction. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor levels were normal while interleukin-6 was elevated. The patient had no evidence of infection. The leukemoid reaction correlated with tumor response.

Conclusion This is the first case report in the English literature of a leukemoid paraneoplastic syndrome in a patient with pancreatic cancer. A clear correlation between tumor response, serum carbohydrate antigen 19-9 levels and leukemoid reaction is documented.

INTRODUCTION

Although only 28,000 cases are diagnosed annually, pancreatic cancer is the fifth leading cause of cancer-death in the US. Symptoms upon diagnosis include abdominal pain (80%); anorexia (65%); weight loss (60%) and jaundice (50%). Paraneoplastic syndromes have been less commonly described. These include panniculitis-arthritis-eosinophilia, dermatomyositis, recurrent Trousseau's syndrome and Cushing's syndrome.

Leukemoid reaction refers to a reactive leukocytosis and has been described in response to inflammation, severe or disseminated infection, tissue destruction or other marrow stimulants. Leukemoid reactions have been described mainly in association with lung, gastrointestinal, genitourinary and head and neck cancers [1, 2, 3, 4, 5]. These reactions have been attributed to increased cytokine production. Cytokines implicated in this process include granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), interleukin 3 (IL-3) and interleukin 6 (IL-6) [5, 6, 7, 8, 9, 10, 11].

Leukemoid reactions have rarely been described in association with pancreatic cancer. To our knowledge, this is the fourth case to be reported in literature. Furthermore, this is the only case described that shows an unequivocal tumor response and leukemoid reaction correlation.

CASE REPORT

A 47-year-old man presented with a history of 3.5 kg weight loss and pain in his right upper quadrant and shoulder of 2-month duration. Subsequent imaging studies revealed a mass

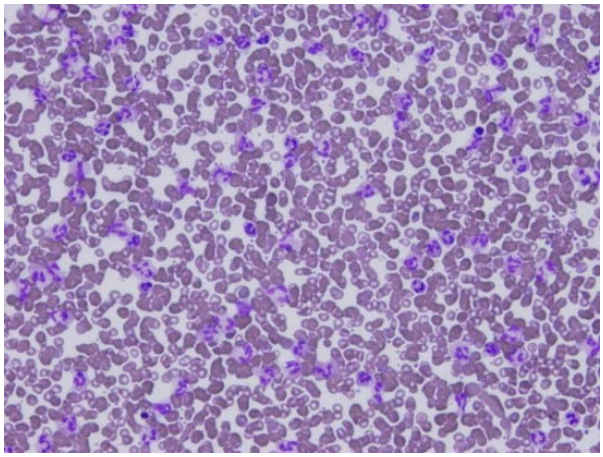

Figure 1. Peripheral smear shows marked granulocytosis without any bands, myelocytes or metamyelocytes. H&E stain.

in the body of the pancreas and metastatic disease to the liver. An ultrasound-guided biopsy of the liver was performed and confirmed a metastatic moderately to poorly differentiated adenocarcinoma of pancreatic origin. His initial WBC count was 30,300 cells/mm^3 and his peripheral smear (Figure 1) showed marked granulocytosis without any bands, myelocytes, or metamyelocytes. His leukocyte alkaline phosphatase (LAP) score was 202 (reference range: 50-100) suggesting a non-malignant myeloproliferative process. Septic work-up, including chest X-ray, urine culture, and blood cultures was negative. G-CSF and GM-CSG were within normal range while IL-6 level was elevated at 27 pg/mL (reference range: 0-12 pg/mL).

He was started on palliative chemotherapy with docetaxel and gemcitabine with initial resolution of leukemoid reaction. A

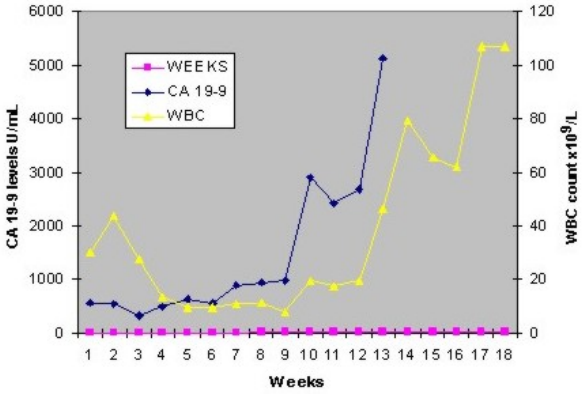

Figure 2. Clinical course: leukocyte counts and CA 19-9 steadily increased after 4 months of chemotherapy and correlated with clinical progression.

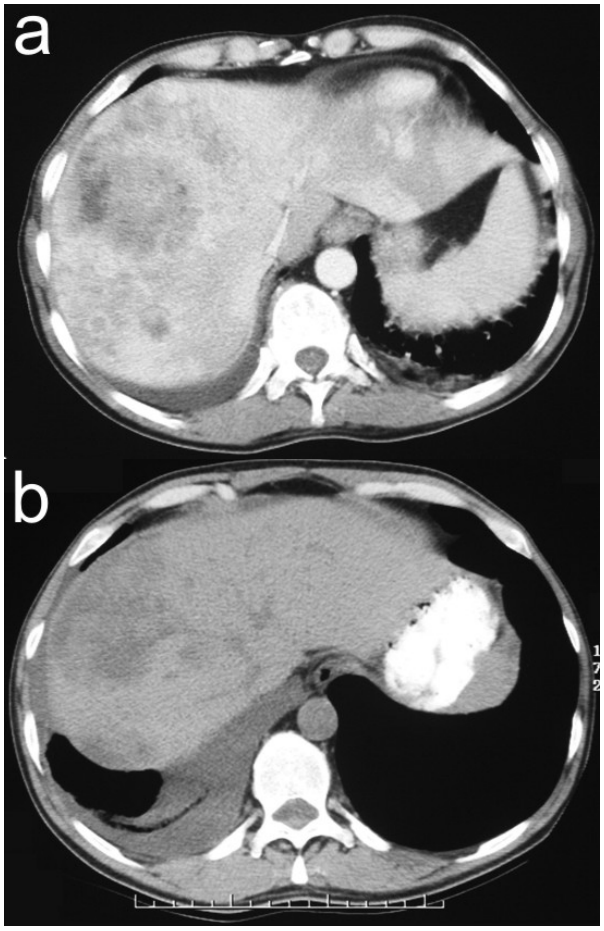

Figure 3. CT images at baseline (**a.**) and after 3 cycles of chemotherapy (**b.**).

correlation between CA19-9 response and white blood cell count (WBC) was noted (Figure 2). An initial decrease in his CA 19-9 levels was associated with normalization of WBC counts as well as disease stabilization on computerized tomography performed after 3 cycles of treatment (Figure 3). Of interest, he never developed any significant leukopenia despite the myelosuppressive nature of docetaxel and gemcitabine combination. As his CA 19-9 increased, his WBC increased despite ongoing chemotherapy. Radiological disease progression was documented after 6 cycles of chemotherapy at which point his WBC exceeded 60.3x10^9 (cells/L). Treatment was discontinued and he died shortly after. His total WBC prior to expiring exceeded 100x10^9 (cells/L).

DISCUSSION

Leukemoid reactions have been rarely described in association with pancreatic

cancer. A review of the literature revealed only three other case reports of leukemoid reactions in pancreatic cancer and in two of those the patients expired shortly after diagnosis [12, 13, 14]. This case, to our knowledge, is the first case described in the English literature.

Leukemoid reactions in advanced malignancy are usually myelocytic although eosinophilia, basophilia or monocytosis may be seen. On the peripheral smear, orderly progressive granulocyte maturation is noted and there are usually no blasts or nucleated red cells. The leukemoid reaction is distinguished from chronic myelogenous leukemia by an increased leukocyte alkaline phosphatase, and generally, lack of thrombocytopenia.

The mechanisms of cancer-associated leukemoid reactions are under study. There are various reports in the literature of elevations in GM-CSF, G-CSF, IL-3 or IL-6 in tumors of the nasopharynx, kidneys and bladder [5, 6, 7, 8, 9, 10, 11].

In this particular case, leukocytosis represented a true leukemoid reaction as suggested by the elevated LAP and lack of a left shift on the WBC differential. An infectious etiology is unlikely given the negative septic work-up. The paraneoplastic etiology is confirmed by the strong inverse correlation between tumor response and leukocytosis. It is highly likely that tumor progression and necrosis may be associated with an increase in inflammatory cytokine response resulting in leukocytosis. The possibility of a direct secretion of cytokines by the tumor leading to a leukemoid reaction is also a distinct possibility. Although some reports implicated G-CSF [7, 9, 15] or GM-CSF [5, 6] in paraneoplastic leukemoid reactions, this is unlikely to be the case in our patient since his G-CSF and GM-CSF levels were within normal range. It is not clear that the moderate IL-6 elevation had a significant role in inducing the leukemoid reaction, but this remains a distinct possibility since this interleukin has been associated with leukemoid reactions [10, 11]. Other factors secreted directly by the tumor or related to an inflammatory process may also have had a contributory role. The identification of such factors may have prognostic as well as therapeutic implications.

Received June 24th, 2006 - Accepted August 24th, 2006

Keywords Interleukin-6; Leukemoid Reaction; Pancreatic Neoplasms

Abbreviations CA: carbohydrate antigen; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IL: interleukin; LAP: leukocyte alkaline phosphatase

Correspondence
Marwan G Fakih
Department of Medicine
Roswell Park Cancer Institute
Elm and Carlton Sts
Buffalo, NY 14263
USA
Phone: +1-716.845.8189; +1-716.845.3362
Fax: +1-716.845.8008
E-mail: marwan.fakih@roswellpark.org

References

1. Nimieri HS, Makoni SN, Madziwa FH, Nemiary DS. Leukemoid reaction response to chemotherapy and radiotherapy in a patient with cervical carcinoma. Ann Hematol 2003; 82:316-7. [PMID 12739065]

2. Ganti AK, Potti A, Mehdi S. Uncommon syndromes and treatment manifestations of malignancy: Case 2. Metastatic non-small-cell lung cancer presenting with leukocytosis. J Clin Oncol 2003; 21:168-70. [PMID 12506187]

3. Stav K, Leibovici D, Siegel YI, Lindner A. Leukemoid reaction associated with transitional cell carcinoma. Isr Med Assoc J 2002; 4:223-4. [PMID 11908271]

4. Saussez S, Heimann P, Vandevelde L, Bisschop P, Jortay A, Schandene L, Cogan E. Undifferentiated carcinoma of the nasopharynx and leukemoid reaction: report of case with literature review. J Laryngol Otol 1997; 111:66-9. [PMID 9292137]

5. Wetzler M, Estrov Z, Talpaz M, Markowitz A, Gutterman JU, Kurzrock R. Granulocyte-macrophage colony-stimulating factor as a cause of paraneoplastic leukaemoid reaction in advanced transitional cell

carcinoma. J Intern Med 1993; 234:417-20. [PMID 7691980]

6. Watanabe M, Ono K, Ozeki Y, Tanaka S, Aida S, Okuno Y. Production of granulocyte-macrophage colony-stimulating factor in a patient with metastatic chest wall large cell carcinoma. Jpn J Clin Oncol 1998; 28:559-62. [PMID 9793030]

7. Sato K, Terada K, Sugiyama T, Sugiyama T, Masuda H, Kakinuma H, et al. Granulocyte colony-stimulating factor produced by bladder carcinoma of a patient with leukemoid reaction did not affect proliferation of the tumor cells. J Urol 1994; 151:1687-90. [PMID 7514696]

8. Nakada T, Sato H, Inoue F, Mizorogi F, Nagayama K, Tanaka T. The production of colony-stimulating factors by thyroid carcinoma is associated with marked neutrophilia and eosinophilia. Intern Med 1996; 35:815-20. [PMID 8933194]

9. Chen YM, Whang-Peng J, Liu JM, Chao Y, Lai CR, Wang SY et al. Leukemoid reaction resulting from multiple cytokine production in metastatic mucoepidermoid carcinoma with central necrosis. Jpn J Clin Oncol 1995; 25:168-72. [PMID 7545252]

10. Hisaoka M, Tsuji S, Hashimoto H, Aoki T, Uriu K. Dedifferentiated liposarcoma with an inflammatory malignant fibrous histiocytoma-like component presenting a leukemoid reaction. Pathol Int 1997; 47:642-6. [PMID 9311018]

11. Melhem MF, Meisler AI, Saito R, Finley GG, Hockman HR, Koski RA. Cytokines in inflammatory malignant fibrous histiocytoma presenting with leukemoid reaction. Blood 1993; 82:2038-44. [PMID 7691245]

12. Godquin B. Cancer of the pancreas and paraneoplastic leukemoid syndrome. Chirurgie 1973; 98:785-7. [PMID 4711525]

13. Akoun G, Duhamel G, Duvaldestin P, Koubi G, Brocard H. Myeloid leukemoid reaction in cancer of the pancreas: paraneoplastic syndrome or myeloid leukosis? Sem Hop 1972; 48:861-3. [PMID 4339445]

14. Akoun G, Duhamel G, Duvaldestin P, Koubi G, Brocard H. Paraneoplastic leukemoid reaction of a myeloid type or myeloid leukemia in cancer of the pancreas? Presse Med 1971; 79:2327. [PMID 5288840]

15. Tachibana M, Miyakawa A, Tazaki H, Nakamura K, Kubo A, Hata J, et al. Autocrine growth of transitional cell carcinoma of the bladder induced by granulocyte-colony stimulating factor. Cancer Res 1995; 55:3438-43. [PMID 7542171]