

## Anaplastic Large Cell Lymphoma with Involvement of the Pancreas Presenting as Panniculitis in a Patient with a History of Acute Myeloid Leukemia - Case Report and Review of the Literature

**A 66-year-old man with history of acute myeloid leukemia (AML) presented with B-symptoms and abdominal pain. A CT scan of the abdomen demonstrated an enlargement of the head and uncinate of pancreas and diffuse lymphadenopathy. The patient developed respiratory distress and expired. An autopsy of the pancreas revealed clusters of large, atypical cells, which morphologically and immunophenotypically were consistent with CD-30 positive, ALK-negative anaplastic large cell lymphoma (ALCL) of T-cell lineage and multifocal fat necrosis (panniculitis) in the peripancreatic adipose tissue. This is the first case of ALCL of the pancreas and panniculitis in a patient with history of AML.**

*Haematologica* 2006; 91:(11)e150-e152

Primary neoplasms of the pancreas are mostly adenocarcinomas. Non-Hodgkin's lymphoma (NHL) involving the pancreas is uncommon, and pancreatic anaplastic large cell lymphoma (ALCL) is rare.<sup>1</sup> Here we describe the first case of ALCL of the pancreas presenting as mesenteric panniculitis in a patient with acute myeloid leukemia (AML) in complete remission, and we also review the relevant literature.

### Case report

A 66-year-old man from Middle East with a history of AML presented to The University of Texas M. D. Anderson Cancer Center with fever. He had been diagnosed with AML with normal cytogenetics in September 2001 at M. D. Anderson Cancer Center and had received induction chemotherapy with idarubicin and cytarabine followed by six courses of consolidation therapy, including cytarabine and gemtuzumab ozogamycin. He had been in complete remission for 4 years when, in December 2005, he began experiencing epigastric discomfort, high-grade fever (38°C), night sweats, chills and weight loss (at 2 months, 7 kg, > 10 percent of his body weight). An extensive workup done by his home physician, including bone marrow aspiration and biopsy, was normal, with the exception of a computed tomography (CT) scan of the abdomen, which showed haziness and stranding in the root of the mesentery (Figure 1A) and led to the diagnosis of mesenteric panniculitis. The patient was treated with high-dose intravenous steroids (prednisone 70 mg daily for 1 month) and intravenous cyclosporine (2 doses, 150 mg each). However, he remained febrile and returned to M. D. Anderson in February 2006 for further evaluation and treatment. The hemoglobin level was 11.8 g/dL, the leukocyte count was 15.9 k/ $\mu$ L (neutrophils 87%, lymphocytes 12%, basophils 1%), and the platelet count was 238 k/ $\mu$ L. Blood workup was remarkable for elevated levels of lipase (364 IU/L; upper limit of normal [ULN] = 300 IU/L),  $\gamma$ -microglobulin (4.3 mg/L; ULN = 1.8 mg/L), and lactate dehydrogenase (969 IU/L; ULN = 618 IU/L). Alpha 1 antitrypsin deficiency screening test was negative. A bone marrow aspiration and biopsy confirmed that the AML remained in complete remission and did not show any abnormal cells. A CT scan of the abdomen showed that the head and uncinate of pancreas were larger and the lymph

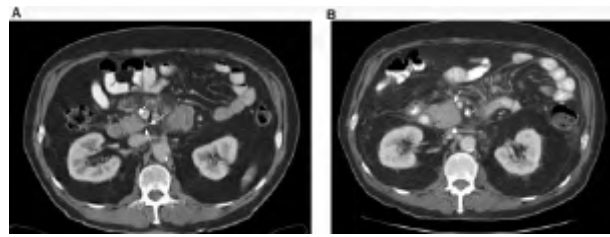


Figure 1.

Figure 2.

nodes were more rounded and increased compared to the prior CT scan images (time difference, 2 months) (Figure 1B). Multiple small nodes in the mesentery, and loss of normal soft tissue planes involving the mesentery were also noted. The steroid dosage was tapered, a gastrointestinal consultation was obtained, and a biopsy of the head of the pancreas was scheduled.

On the day of the scheduled biopsy, the patient presented to the clinic with high-grade fever, hypotension, dehydration, and epigastric pain, and he was admitted to the hospital. Two days into the hospital stay, the patient developed progressive shortness of breath and hypoxemia and, therefore, was transferred to the intensive care unit. A CT scan of the chest showed interstitial and alveolar infiltrates in both lungs, with accompanying effusion, and he was started on piperacillin-tazobactam. General surgery was consulted for laparoscopic biopsy, but they declined to perform the procedure in view of the worsening respiratory status of the patient. The differential diagnoses at this stage included pancreatitis, lymphoma, pancreatic cancer, chloroma, tuberculosis or idiopathic mesenteric panniculitis, which is a diagnosis of exclusion. Serum and bronchoalveolar lavage tests were positive for cytomegalovirus antigen, whereas all other cultures, including blood cultures were negative. Despite broad antimicrobial coverage with ganciclovir, meropenem, linezolid, doxycycline, and voriconazole, the patient developed severe respiratory distress requiring emergent intubation. His condition continued to deteriorate with desaturation and hypotension and thirteen days after being admitted to the hospital, the patient died.

An autopsy restricted to biopsy of the pancreas was granted. Because exposure was limited to an incision of the upper abdominal wall, it is probable that the tissue biopsied was from the body or the tail of the pancreas and soft tissue anterior to this organ and not from the head of the pancreas. Gross examination revealed a firm, irregular, fibrotic pancreas with areas of hemorrhage and

**Table 1.** Clinical presentation and outcomes of reported cases with anaplastic large cell lymphoma of the pancreas.

	Age/Gender	Presentation	Treatment	LDH	$\beta_2M$	ALK	Outcome
Present study	66/M	Fever, weight loss, abdominal pain	Glucocorticoids (prior to diagnosis)	High	High	Negative	Death before the diagnosis
Savopoulos <i>et al.</i> <sup>5</sup>	80/M	Fever, anorexia, weight loss	Glucocorticoids (prior to diagnosis)	High	High	Negative	Death 2 days after laparotomy for diagnosis
Chim <i>et al.</i> <sup>6</sup>	27/F	Abdominal pain, weight loss	CHOP	Normal	NR	Positive	Partial remission Progression and death
Fraser <i>et al.</i> <sup>7</sup>	13/M	Epigastric pain, vomiting, weight loss ifosfamide, cytarabine, doxorubicin, methotrexate	Cyclophosphamide, dexamethasone,	High	NR	at 6 months Positive	Disease-free survival (DFS): 12 months
Parwani <i>et al.</i> <sup>8</sup>	30/M	Abdominal pain, vomiting, weight loss	Not treated	Normal	NR	Positive	NR
Cohen <i>et al.</i> <sup>9</sup>	29/M	Abdominal pain, gastrointestinal bleeding with pain	Whipple's operation, CHOP	Normal	NR	Positive	DFS: 30 months
Castellanos <i>et al.</i> <sup>10</sup>	24/F	Vomiting, abdominal pain, subcutaneous nodules	ProMACE, CytaBO	NR	NR	Positive	DFS: 27 months
Maruyama <i>et al.</i> <sup>11</sup>	46/F	Abdominal pain, jaundice	Whipple's operation MACOP-P	NR	NR	Positive	DFS: 18 months

Abbreviations: LDH: lactate dehydrogenase level,  $\beta_2M$ :  $\beta_2$ -microglobulin level, ALK: anaplastic lymphoma kinase, M: male, F: female, CHOP: cyclophosphamide, adriamycin, vincristine, and prednisone, NR: not recorded, ProMACE: prednisone, methotrexate, adriamycin, cyclophosphamide, and etoposide, CytaBOM: cytosine arabinoside, etoposide, bleomycin, vincristine, and methotrexate, MACOP-P: methotrexate, adriamycin, cyclophosphamide, vincristine, prednisone, and peplomycin.

parenchymal fibrosis. Adjacent peripancreatic adipose tissue showed areas of fat necrosis and hemorrhage. Histologic sections showed clusters of large, atypical cells in peripancreatic connective tissue, with invasion of vascular/lymphatic channels in some areas. The atypical cells were pleomorphic and had features of neoplastic cells (Figure 2A, hematoxylin and eosin stain, x 400). They were present infiltrating the connective tissue of neurovascular structures between pancreatic lobules and focally within the pancreas. Multifocal fat necrosis (panniculitis) was also present in peripancreatic tissue. The atypical cells were positive for CD2, CD4, CD30 (Figure 2B, x 400), CD5 (Figure 2C, x 400), epithelial membrane antigen and granzyme B (Figure 2D, x 400), and negative for CD3, CD8, CD20, CD38, CD43, CD45, CD117, myeloperoxidase, lysozyme, anaplastic lymphoma kinase (ALK), S-100, keratin, PAX-5 and alpha fetoprotein. Antibody against CD68 highlighted many histiocytes. Anti-human chorionic gonadotropin staining was positive in some of the degenerative large cells. Stains for immunoglobulin kappa and lambda light chains were inconclusive. Stains with periodic acid Schiff revealed no glycogen or mucin deposition. In situ hybridization for Epstein-Barr virus antigen was negative. The morphologic and immunophenotypic were consistent with CD-30-positive, ALK-negative, anaplastic large cell lymphoma of T cell lineage.

#### Discussion

Anaplastic large cell lymphomas were first described in 1985 and account for approximately 2% of NHL in adults.<sup>2</sup> Malignant cells intensely and uniformly express CD30 antigen and either T cell- or no lineage-specific antigens. The diagnosis is based on morphological and immunohistochemical findings, and the tumor is further characterized by ALK protein expression.<sup>3</sup> ALCL cases

that are ALK negative are widely regarded to represent a heterogenous group. If strict criteria for diagnosis are used, diagnosis is restricted to cases morphologically and immunophenotypically indistinguishable from those with ALK-positive cells. The entity is still recognized in the current World Health Organization classification.<sup>4</sup>

To our knowledge, only seven cases of pancreatic ALCL have been reported previously (Table 1).<sup>5-11</sup> Although there is a possibility that our patient's lymphoma could have arisen from mesenteric nodes and involved the pancreas by contiguous involvement instead of being of primary pancreatic origin, we believe that this is the first case of pancreatic ALCL reported in a patient with a history of a hematological malignancy.

Clinical presentation of pancreatic ALCL can be summarized as follows: abdominal pain (88%), B-symptoms (62%), weight loss (62%), and fever (25%). Most of the patients were young adults, but one was a pediatric patient<sup>7</sup> and another was 80 years old.<sup>5</sup> The 80-year-old patient was the only one besides our case who did not express ALK protein. His disease had a similar clinical presentation (fever), and outcome, and the patient was treated similarly, with glucocorticoids, prior to the diagnosis. Most of the younger patients with ALK-positive disease were treated with cytotoxic chemotherapy and responded to treatment.<sup>6</sup>

ALCL has been reported to be associated with a more favorable prognosis in patients who are younger and have normal LDH levels, low International Prognostic Index scores,<sup>12</sup> and CD56 negativity,<sup>13</sup> and all of these factors are associated with the expression of ALK. ALCL has traditionally been treated with cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone (CHOP) or third-generation chemotherapy regimens, and occasionally high-dose chemotherapy and autologous stem cell transplantation have been used in the first remis-

sion.<sup>14</sup> In a prospective trial of 15 patients with ALCL treated with high-dose chemotherapy followed by autologous stem cell transplantation, prolonged remission was induced in 90% of patients, with acceptable toxicity and no relapses.<sup>15</sup> However, in this small series, 7 of 15 patients were ALK-positive, which probably represents a clinical entity that has a much better prognosis than patients with ALK-negative disease. Novel therapies, such as with anti-CD30 monoclonal antibody, are being developed for ALCL.<sup>16</sup>

The association between AML and other malignancies has been well described and is thought to be due to genetic predisposition. Also, previous chemotherapy is associated with an increased risk of chromosomal damage.<sup>17-18</sup> Notably, the patient in the current report had received steroids and cyclosporine prior to his presentation at M. D. Anderson. The immunosuppression induced by these agents most likely contributed to CMV viremia and, therefore, to fatal multiorgan failure. The association between CMV infections and calcineurin inhibitors such as cyclosporine is well established in the literature.<sup>19</sup> In addition to ALCL, panniculitis was also evident in the biopsy of the peripancreatic fat of our patient. Patients with panniculitis may benefit from treatment with a somatostatin analogue that sharply attenuates pancreatic exocrine secretion, complete bowel rest, and total parenteral nutrition. We speculate that in our case, pancreatic leakage secondary to pancreatitis and lymphoma could have been responsible for both the necrosis noted in the gross examination of the peripancreatic fat and the acute deterioration of the respiratory status of the patient owing to destruction of the alveoli by pancreatic enzymes.

In summary, this case stresses the importance of an early histologic diagnosis in a patient with a pancreatic mass, when malignancy is suspected. This can easily be performed with endoscopic ultrasound guidance. A clinical presentation of abdominal pain and B-symptoms should raise the suspicion of a pancreatic lymphoma, even though its occurrence is rare. An accurate diagnosis is crucial for determining the correct treatment, i.e., chemotherapy for lymphoma versus radical surgery for a resectable adenocarcinoma.

Bilal Ahmed,<sup>1</sup> Elihu Estey<sup>1</sup>, John Manning,<sup>2</sup> Cynthia David,<sup>3</sup> Michael J. Keating,<sup>1</sup> Hagop Kantarjian<sup>1</sup>, and Apostolia-Maria Tsimberidou<sup>1</sup>

Departments of <sup>1</sup>Leukemia, <sup>2</sup>Hematopathology, and <sup>3</sup>Radiology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

*Acknowledgements: We would like to thank Dr. Cameron Yin for taking the images, Mark Brandt and Ana Martinez for their assistance with the medical graphics, and Vickie Neal for her assistance with the preparation of the manuscript.*

*Key Words: pancreas, lymphoma, anaplastic, large cell*

*Correspondence: Apostolia M. Tsimberidou, M.D., Ph.D.*

*Department of Leukemia, Unit 428, The University of Texas M. D.*

*Anderson Cancer Center 1515 Holcombe Blvd., Houston, Texas 77030*

*Tel: 713.792.4259, Fax: 713.794.4297, E-mail:atsimber@mdanderson.org*

## References

- Salvatore JR, Cooper B, Shah I, Kummert T. Primary pancreatic lymphoma: a case report, literature review, and proposal for nomenclature. *Med Oncol* 2000; 17:237-7.
- Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol* 1998; 16:2780-95.
- Kodet R, Mrhalova M, Krskova L, Stejskalova E. [Anaplastic large-cell lymphoma: review]. 2003; *Cesk Patol* 39:102-14.
- Delsol G, Ralfkiaer E, Stein H, Wright D, Jaffe E. Anaplastic large cell lymphoma. In: Jaffe ES, Stein H, Wardiman JW, eds. Tumors of haematopoietic and lymphoid tissues. World Health Organization classification of tumors. Lyon: IARC Press 2001; 230-5.
- Savopoulos CG, Tsesmeli NE, Kaiafa GD, Zantidis AT, Bobos MT, Hatzitolios AI, et al. Primary pancreatic anaplastic large cell lymphoma, ALK negative: a case report. *World J Gastroenterol* 2005; 11:6221-4.
- Chim CS, Ho J, Ooi GC, Choy C, Liang R. Primary anaplastic large cell lymphoma of the pancreas. *Leuk Lymphoma* 2005; 46:457-9.
- Fraser CJ, Chan YF, Heath JA. Anaplastic large cell lymphoma of the pancreas: a pediatric case and literature review. *J Pediatr Hematol Oncol* 2004; 26:840-2.
- Parwani AV, Kulesza P, Erozan YS, Ali SZ. Pathologic quiz case: a 30-year-old man with lower abdominal and back pain. Anaplastic large cell lymphoma (Ki-1 lymphoma) of the pancreas. *Arch Pathol Lab Med* 2004; 128:e179-80.
- Cohen Y, Libster D, Amir G, Hiller N, Da'as N, Ben Yehuda D, et al. Primary ALK positive anaplastic large cell lymphoma of the pancreas. *Leuk Lymphoma* 2003; 44:205-7.
- Castellanos G, Bas A, Pinero A, Soria T, Parrilla P. Anaplastic large cell lymphoma (CD30, p80+) presenting as acute pancreatitis with subcutaneous nodules. *Eur J Haematol* 1999; 63:205-6.
- Maruyama H, Nakatsuji N, Sugihara S, Atsumi M, Shimamoto K, Hayashi K, et al. Anaplastic Ki-1-positive large cell lymphoma of the pancreas: a case report and review of the literature. *Jpn J Clin Oncol* 1997; 27:51-7.
- ten Berge RL, Dukers DF, Oudejans JJ, Pulford K, Ossenkoppele GJ, de Jong D, et al. Adverse effects of activated cytotoxic T lymphocytes on the clinical outcome of nodal anaplastic large cell lymphoma. *Blood* 1999; 93:2688-96.
- Suzuki R, Kagami Y, Takeuchi K, Kami M, Okamoto M, Ichinohasama R, et al. Prognostic significance of CD56 expression for ALK-positive and ALK-negative anaplastic large-cell lymphoma of T/null cell phenotype. *Blood* 2000; 96:2993-3000.
- Shulman LN, Frisard B, Antin JH, Wheeler C, Pinkus G, Magauran N, et al. Primary Ki-1 anaplastic large-cell lymphoma in adults: clinical characteristics and therapeutic outcome. *J Clin Oncol* 1993; 11:937-42.
- Deconinck E, Lamy T, Foussard C, Gaillard F, Delwail V, Colombat P, et al. Autologous stem cell transplantation for anaplastic large-cell lymphomas: results of a prospective trial. *Br J Haematol* 2000; 109:736-42.
- Zhang M, Yao Z, Zhang Z, Garmestani K, Goldman CK, Ravetch JV, et al. Effective therapy for a murine model of human anaplastic large-cell lymphoma with the anti-CD30 monoclonal antibody, HeFi-1, does not require activating Fc receptors. *Blood* 2006 -- In press.
- Pagana L, Pulsoni A, Tosti ME, Avvisati G, Mele L, Mele M, et al. Clinical and biological features of acute myeloid leukaemia occurring as second malignancy: GIMEMA archive of adult acute leukaemia. *Br J Haematol*. 2001;112:109-17.
- McLaughlin P, Estey E, Glassman A, Romaguera J, Samaniego, F, Ayala, A, et al. Myelodysplasia and acute myeloid leukemia following therapy for indolent lymphoma with fludarabine, mitoxantrone, and dexamethasone plus rituximab and interferon alpha. *Blood*. 2005;105:4573-5.
- Campino A. Gancyclovir prophylaxis in high risk patients. *Transplant Proc*. 2005;37:4311-12.