

## Cystic fibrosis with acute myelogenous leukemia

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Hematologic malignancies including acute leukemias rarely associate with cystic fibrosis (CF). In this paper, we describe a case who was diagnosed with CF when she was three months old and presented with acute myelogenous leukemia (AML) at the age of 17 years. Although she received reduced doses of chemotherapy because of her clinical status she responded well. She is the first CF patient who developed AML in our department among 296 CF patients over a 22-year period.

**Key words:** acute myeloblastic leukemia, children, cystic fibrosis.

Cystic fibrosis (CF) is one of the most frequent genetic diseases in Caucasians. Its clinical manifestations are highly variable, ranging from a characteristic life-shortening pathology of the lungs and the pancreas in classical CF to milder forms that were diagnosed at older ages. Mutational heterogeneity and environmental factors appear responsible for the highly variable involvement of the lung, pancreas, and other organs.

Epidemiologic studies indicate that the overall risk of malignancy among patients with CF is similar to that of the general population. However, recent studies and case reports suggest an increased risk for the development of gastrointestinal malignancies among adult CF patients, particularly of the small bowel, colon, and biliary tract<sup>1-3</sup>. This increased risk appeared to be more pronounced in patients who underwent an organ transplantation<sup>3</sup>. On the other hand, hematologic malignancies including acute leukemias rarely associate with CF and may occur as a late complication<sup>4-6</sup>.

Here, we report a case of a female CF patient with acute myeloid leukemia (AML).

### Case Report

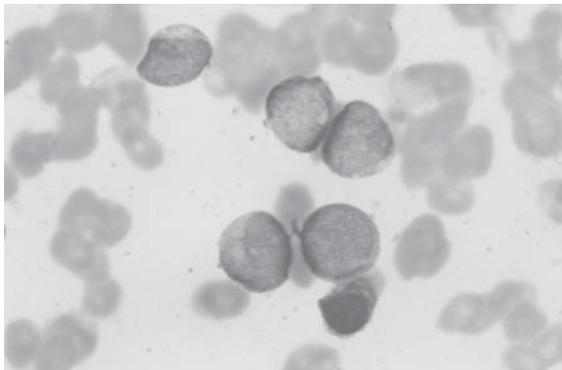
A 17-year-old girl was diagnosed as CF at three months of age with the complaints of persistent diarrhea and cough, and was treated with pancreatic enzyme replacement, antibiotics, mucolytics, chest physiotherapy

and polyvitamin. The genetic analysis showed a W496/2181 del A, 2183 A-G mutation. She suffered from numerous recurrent pulmonary infections that required hospitalization. At the age of 7 years she underwent liver biopsy for parenchymal heterogeneity and macronodularity on abdominal ultrasonography. Liver biopsy revealed chronic parenchymal liver disease consistent with CF. Her nasal polyps were removed surgically at the age of 9 years and two years later rectal prolapse occurred, which did not require surgical repair. From the age of 12 years, CF-related diabetes developed and she required insulin treatment.

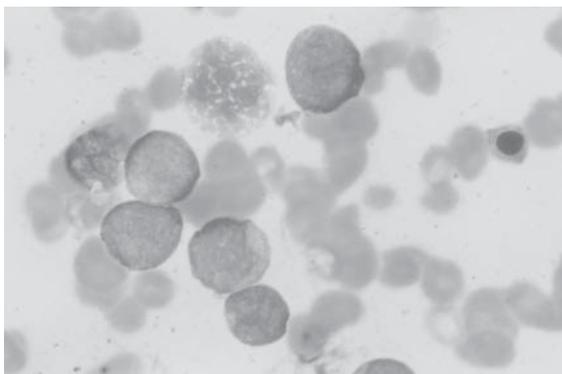
She was previously consulted with the Hematology Department because of thrombocytopenia and massive splenomegaly at the age of 15 years. Although her clinical and laboratory findings might have suggested hypersplenism due to the massive splenomegaly, bone marrow aspiration was done. At that time bone marrow aspirate was hypercellular with no blasts.

She was admitted to the hospital at the age of 17 because of a persistent fever and neutropenia and was treated with antibiotics. Her sputum culture was positive for *Pseudomonas aeruginosa*. At that time, computerized tomography of her lungs revealed bilateral bronchiectasis and pulmonary infiltration. Ten days later, progressive weakness and fatigue with persistent fever occurred. Her physical findings were normal except for pallor and hepatosplenomegaly (hepatomegaly 2 cm,

splenomegaly 20 cm from the costal margins). Laboratory results included a hemoglobin level of 7.6 g/dl, white blood cell count of  $0.9 \times 10^9/L$  with 5% blasts and platelet count of  $6 \times 10^9/L$ . Evaluation of the peripheral blood smear showed prominent macrocytosis with anisocytosis and abnormal nucleated, giant myeloblasts, with distorted nuclear and cytoplasmic maturation. Bone marrow examination revealed a cellular marrow with 59% immature myeloid blasts, some containing Auer rods. Flow cytometric analysis of surface markers of BM blasts expressed CD45 (91%), CD33 (57%), CD34 (77%), CD19 (69%), HLA-DR (88%), and CD15 (46%). She was diagnosed as having AML-M2 (Fig. 1).



(a)



(b)

Fig 1. (a) Bone marrow smear at diagnosis; (b) Blast cells from a CF patient with AML-M2.

The bone marrow karyotype was normal. Institutional AML protocol was started<sup>7</sup>. Because of her altered clinic status and pulmonary hypertension, chemotherapy doses were reduced. Bone marrow aspiration was obtained at the end of two week of induction therapy and complete response was diagnosed with 1% blast,

20% normoblast, 26% metamyelocyte, 17% myelocyte, 22% promyelocyte, 6% neutrophil, and 8% lymphocytes. HLA identical donor was not found for bone marrow transplantation. She remained well during treatment with no acute pulmonary exacerbations for two months. However, six months after the diagnosis while under maintenance treatment, she suffered extensive pulmonary fungal infection and died due to septicemia and multiorgan failure.

### Discussion

Cancer in patients with CF has been a rare event according to the literature. Improved outcome with supportive treatment can allow survival of CF patients beyond the second decade. Despite the prolonged survival, overall risk of malignancy does not increase among patients with CF. Three epidemiologic studies evaluated the risk of malignancy in patients with CF. Sheldon et al.<sup>1</sup> observed a possible association of CF with specific gastrointestinal cancers, and they concluded that there was an overall increase in cancer risk. Neglia et al.<sup>2</sup> reported that the overall risk of cancer is similar to that of the general population. They demonstrated an increased risk of gastrointestinal malignancies (esophagus, stomach, small and large bowel, liver and biliary tracts, pancreas tumors). In recent data, Maisonneuve et al.<sup>3</sup> compared transplanted and nontransplanted CF patients with the expected population-based cancer incidence data, and observed an increased risk of digestive tract cancers among adult CF patients that was more pronounced in organ-transplanted patients. No overall development of cancer in the CF population after removal of gastric malignancies was reported in the study.

The association of CF and acute leukemia is extremely rare. Maisonneuve et al.<sup>3</sup> reported 11 leukemia patients with CF while 7.2 was expected (standardized incidence ratio [SIR]=1.5, 95% confidence interval [CI]=0.8 to 2.7). To our knowledge, five cases with acute lymphoblastic leukemia (ALL) and three cases with AML have been reported in the literature<sup>4-6,8,9</sup>. In this paper, we describe a case who was diagnosed with CF when she was three months old and presented with AML at the age of 17 years. In our department, 296 patients were diagnosed with CF over a period of 22 years. This is the first AML case in our

clinic with CF. Although she received reduced doses of chemotherapy, she responded well and no side effects were seen during the therapy period. However, she died while in remission because of infection complication.

The development of most cancers is related to both environmental and genetic factors. However, host factors are also important in the development of hematologic malignancies in childhood. In most cases, the precise cause of malignancies is unknown. The specific reason or reasons for the association between CF and hematologic malignancies remains a mystery but herein we discuss some interesting details that have been pointed out previously.

The risk of pancreatic cancer in CF patients was associated with chronic pancreatitis. Chronic inflammation appears to increase genomic damage and cellular proliferation by various cytokines, reactive oxygen species, and mediators of the inflammatory pathway (e.g., nuclear factor [NF]- $\kappa$ B and cyclooxygenase-2), which increase cell cycling, cause loss of tumor suppressor function and stimulate oncogene expression, and these favor malignant transformation of pancreatic cells that may lead to pancreatic malignancy<sup>10,11</sup>. Recurrent and persistent infections in CF may also facilitate the risk of hematologic malignancies. However, we know that inflammation alone usually does not lead to cancer.

The carrier frequency of CF is relatively high (5%). Previous reports suggested that carriers of the  $\Delta$ F508 mutation may have an increased risk of developing AML. They speculate that this could happen through the direct effect of the CF gene itself, or through its influence on another gene, such as the met oncogene, or gene(s) involved in granulocyte function on the long arm of chromosome 7<sup>12</sup>. However, a recent study showed that there was no increase in the risk of having AML in the relatives who carried the  $\Delta$ F508 mutation. On the other hand, 786 leukemic patients that were analyzed for the carrier frequency were not significantly different from the control group<sup>13</sup>.

The CF gene lies in chromosome region 7q31. Monosomy or deletion of chromosome 7 is a frequent finding in both AML and myelodysplastic syndromes (MDS). It has been suggested that there is a critical region that may connect the two diseases<sup>14</sup>. This channel

protein may function in most human cells to help maintain cellular homeostasis. Intracellular chloride channels have been recognized for their contributions as they can modify cell cycle, apoptosis, cell adhesion and cell motility<sup>15</sup>. Cell cycle control has become particularly relevant to the field of cancer genetics, because several of the important proteins are themselves protooncogenes or tumor suppressors. As the homeostasis of cells is disrupted, uncontrolled proliferation may occur. This needs further investigation in CF patients with AML.

We think that all the explanations for the hematologic malignancies observed in patients with CF are similar to those in a previously healthy child and remain limited.

Successful treatment of pancreatic insufficiency, diabetes, pulmonary disease, and nutrition now allow individuals with CF to live well into their 30s and 40s. This also means that some of these patients now have long-standing CF; thus, we believe that the risk of cancer and AML must be considered in those patients. We report our first CF patient with hematologic malignancy in view of its contribution to the accumulating literature on this topic.

#### REFERENCES

1. Sheldon CD, Hodson ME, Carpenter LM, et al. A cohort study of cystic fibrosis and malignancy. *Br J Cancer* 1993; 68: 1025-1028.
2. Neglia JP, FitzSimmons SC, Maisonneuve P, et al. The risk of cancer among patients with cystic fibrosis. *N Engl J Med* 1995; 332: 494-499.
3. Maisonneuve P, FitzSimmons SC, Neglia JP, Campbell PW 3<sup>rd</sup>, Lowenfels AB. Cancer risk in nontransplanted and transplanted cystic fibrosis patients: a 10-year study. *J Natl Cancer Inst* 2003; 95: 381-387.
4. Biggs BG, Vaughan W, Colombo JL, Sanger W, Purtilo DT. Cystic fibrosis complicated by acute leukemia. *Cancer* 1986; 57: 2441-2443.
5. Rizzari C, Conter V, Jankovic M, et al. Acute lymphoblastic leukaemia in a child with cystic fibrosis. *Haematologica* 1992; 77: 427-429.
6. Miller RW. Childhood cancer and congenital defects: a study of US death certificates during the period 1960-1966. *Pediatr Res* 1969; 3: 389-397.
7. Hicsonmez G, Cetin M, Tuncer AM, et al. Children with acute myeloblastic leukemia presenting with extramedullary infiltration: the effects of high-dose steroid treatment. *Leuk Res* 2004; 28: 25-34.
8. Rizzari C, Conter V. Childhood ALL and cystic fibrosis-treatment and outcome. *Med Pediatr Oncol* 1995; 25: 223.
9. Gururangan S, Horner M, Rodman JH, Marina NM. Successful treatment of acute lymphoblastic leukemia in a child with cystic fibrosis. *Med Pediatr Oncol* 1994; 22: 414-416.

10. Whitcomb DC. Inflammation and cancer V. Chronic pancreatitis and pancreatic cancer. *Am J Physiol Gastrointest Liver Physiol* 2004; 287: 315-319.
11. Farrow B, Evers BM. Inflammation and the development of pancreatic cancer. *Surg Oncol* 2002; 10: 153-169.
12. Al-Jader LN, West RR, Holmes JA, Meredith L, Goodchild MC, Harper PS. Leukaemia mortality among relatives of cystic fibrosis patients. *Arch Dis Child* 1991; 66: 317-319.
13. Padua RA, Warren N, Grimshaw D, et al. The cystic fibrosis delta F508 gene mutation and cancer. *Hum Mutat* 1997; 10: 45-48.
14. Katz F, Webb D, Gibbons B, et al. Possible evidence for genomic imprinting in childhood acute myeloblastic leukaemia associated with monosomy for chromosome 7. *Br J Haematol* 1992; 80: 332-336.
15. Pan J, Bear C, Farragher S, Cutz E, Yeger H. Cystic fibrosis transmembrane conductance regulator modulates neurosecretory function in pulmonary neuroendocrine cell-related tumor cell line models. *Am J Respir Cell Mol Biol* 2002; 27: 553-560.