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CASE REPORT

Pancreatic Lipomatosis in a Patient with Pancytopenia and Hypoplastic Bone Marrow

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ABSTRACT

Pancreatic lipomatosis is the replacement of pancreatic parenchyma by adipose tissue. It is the most common pancreatic lesion encountered, and usually of little clinical significance. Although the exact pathobiology is not known, there are several associated risk factors, such as pancreatitis, obesity, and congenital syndromes. We describe a patient who was previously diagnosed with acute myelogenous leukemia, underwent induction chemotherapy without bone marrow recovery. On presentation to our institution, he was incidentally found to have near complete fatty replacement of the pancreas on computed tomography imaging studies which prompted further evaluation for pancreatic sufficiency. He was subsequently diagnosed with shwachman diamond syndrome. It is necessary for adult physicians to recognize shwachman diamond syndrome as a possible cause of pancreatic lipomatosis, particularly in patients who have cytopenia and hypoplastic bone marrow.

INTRODUCTION

Fat replacement of the pancreas is known by several terms,including pancreatic lipomatosis, pancreatic steatosis, fatty pancreas, and lipomatous pseudohypertrophy. All of which are general terms used to describe fat deposition of the pancreatic parenchyma. Progressive replacement by adipose tissue of the parenchyma of atrophying organs has been previously recognized since 1857, to which Virchow termed "lipomatosis," considering it to be a neoplastic process [1]. The pathobiology of this process is not completely understood; however, there have been many cases describing the conversion of all or part of the pancreas into fat. It has been reported in patients with obstruction of the pancreatic ducts by tumors or stones, affecting the distal portion of the pancreas. It has also been found in patients with diabetes mellitus, metabolic syndrome, or congenital syndromes diffusely affecting the pancreas. Pancreatic lipomatosis in adults most often comes to clinical attention through incidental findings on imaging. We report near complete fatty replacement of the pancreas in a patient with SDS.

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CASE REPORT

A thirty-nine-year-old gentleman with a past medical history of AML diagnosed via bone marrow fine needle aspiration with greater than 20% myeloblasts **(Figure 1),** who underwent induction chemotherapy with cytarabine and idarubicin 18 months prior, presented to our institution to establish care. By World Health Organization, the diagnosis of AML is established by the presence of 20% myeloblasts in the bone marrow or peripheral blood. Following induction chemotherapy, he was deemed not a candidate for consolidation chemotherapy due to multiple life threatening complications including pulmonary aspergillosis, acalculous cholecystitis, chemotherapy related hepatic failure, and persistent pancytopenia with a hypocellular bone marrow on multiple subsequent biopsies. The lack of cellular recovery of the bone marrow following induction chemotherapy was of concern given this is not the natural course of recovery following induction chemotherapy. On presentation to our institution he was noted to have several days of non-productive cough, subjective fevers, chills, and associated chest pain. He was febrile to F° 102.4 on admission, otherwise all other vital signs were stable and within normal limits. Physical examination revealed a well nourished man with short stature and faint left lung crackles. There was no abdominal tenderness or any notable congenital abnormalities. Laboratory studies included: Absolute neutrophil count (ANC), 0.6 K/cumm; platelet (Plt); 34 K/

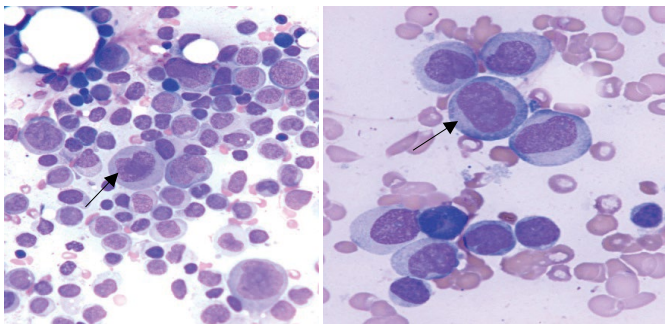

Figure 1. February 2013, Bone marrow FNA with >20% myeloblasts.

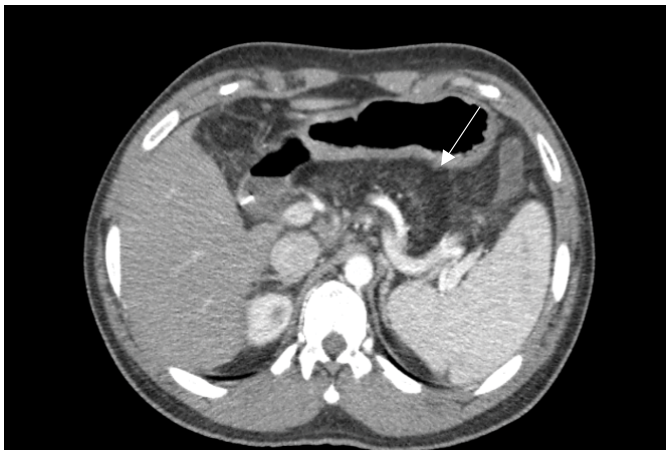

Figure 2. CT Chest revealing for near complete fatty replacement of the pancreas (arrow).

cumm; hemoglobin (Hgb), 12 g/dL, with no blasts seen on peripheral blood smear.

A Computed Tomography chest was obtained to assess for pulmonary infection, the patient was incidentally found have near complete fatty replacement of the pancreas **(Figure 2).** There were no focal masses or areas of pancreatic ductal obstruction noted. After outside hospital records from several months prior to presentation were obtained, it was noted that the patient had an MRI abdomen also revealing for near complete fatty replacement of the pancreas; however, the cause was not found at that time. The finding of near complete fatty replacement of the pancreas along with a persistent hypoplastic marrow following induction chemotherapy **(Figure 3)** was clinically consistent with SDS. Further laboratory testing was performed to assess pancreatic function. All pancreatic enzymes were decreased: elastase, 37mcg/g (normal, >200 mcg/g); amylase, 14U/L (normal, 21-101 U/L); isoenzyme, 4 U/L (normal, 16-46 U/L); serum trypsinogen, <5ng/mL (normal, 19-68 ng/mL). Fat soluble vitamins were as follows: vitamin A, 27 mcg/dL (normal, 38-98 mcg/dL); vitamin D, 24 ng/mL (normal, 30-96 ng/mL); vitamin E, 8.4mg/L (normal, 5.7-19.9mg/L). The clinical scenario of fatty replacement of the pancreas, and persistently hypocellular bone marrow post-induction was consistent with SDS. There were two disease-causing mutations identified in the Swachman-Bodian-Diamond (SBDS) gene in this patient. The first was c.258+2 T>C mutation, which is a common mutation in Swachman-Diamond syndrome because it is present in a nearby SBDS pseudogene which is an inactive gene with many mutations. Sections of the pseudogene are transferred to the SBDS gene, causing Swachman-Diamond syndrome. The other mutation found was c.693delA, a frameshift mutation, causing loss of normal protein function. The presence of these two mutations was consistent with the diagnosis of Swachman-Diamond syndrome [2].

Although other IBMFS (inherited bone marrow failure syndrome) were considered, such as Faconi Anemia, Diamond Blackfan Anemia, and Johanson-Blizzard syndrome, SDS was the leading differential in this patient due to the findings of near complete fatty replacement of the pancreas, along with bone marrow manifestations, and due to its presentation in adulthood in this patient.

The patient denied ever having signs or symptoms of malabsorption or uncontrolled glucose. Since he was not pancreatic insufficient based on history, pancreatic enzyme replacement was not warranted.

He continued to receive granulocyte colony-stimulating factor (G-CSF) for neutropenia and remained on prophylactic anti-microbials (levofloxacin, fluconazole, and acyclovir) until two months after his initial presentation, at which time repeat bone marrow biopsy revealed recurrence of AML with 60% myeloblasts. He was started on low dose fludarabine and cytarabine, as he would not be able to tolerate full dose chemotherapy. This was done as a bridge to allogeneic hematopoietic stem cell transplant.

DISCUSSION

Complete or near complete fatty replacement of the pancreas is an uncommon, often benign entity. The presence of small amounts of adipose tissue in the pancreas is rarely considered pathological. It is the most common degenerative lesion of the pancreas, and has little clinical significance [3]. In fact, it is not an uncommon finding in the obese population; however, this is fat infiltration much like hepatic steatosis, rather than fat replacement, and appears to be reversible with weight reduction. There is

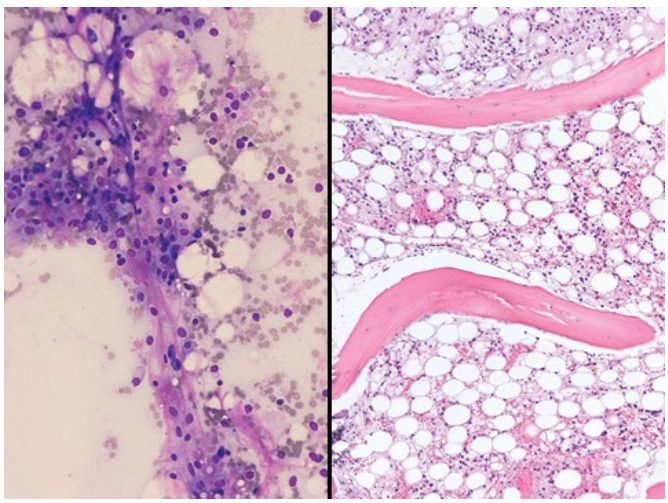

Figure 3. June 2014, Bone marrow aspiration revealing hypocellular bone marrow, low turnover osteoporosis, and immunohistochemical stain showing CD34+ cells (myeloblasts).

a dilemma that exists with using general terms such as fatty pancreas, as such term does not delineate between the accumulation of adipose in the pancreas versus the replacement of the pancreatic parenchyma by adipose tissue as was the case in our patient. Fatty pancreas is a general term for pancreatic fat accumulation. Pancreatic lipomatosis is fatty replacement of the exocrine pancreas, while pancreatic steatosis is fat accumulation in islet or acinar cells [4].

The radiographic features of this condition have been well described and can be diagnosed using CT or MRI. Fatty replacement of the pancreas is the most common lesion affecting the pancreas. Ultrasound is not a useful modality in diagnosing pancreatic lipomatosis due to its limitations of the pancreas being obscured by overlying bowel gas, and the increased echogenicity associated with a fatty pancreas makes it difficult to distinguish from retroperitoneal fat [5]. Unenhanced CT is considerably more reliable in the diagnosis due to the negative attenuation value of the pancreatic tissue replaced by fat [6]. A drawback of CT is it cannot reliably differentiate focal fatty replacement of the pancreas from a true neoplasm. Contrast enhanced CT would not show a negative attenuation value due to normal pancreatic tissue being entrapped between the areas of fatty replacement, which would be contrast enhanced [7]. MRI is best used under these circumstances, and is very useful in demonstrating the nature of a tissue, especially fat. In a brief series of patients with Shwachman Diamond syndrome, MRI had 100% positive predictive value in revealing pancreatic lipomatosis [8].

Although the exact pathobiology of pancreatic parenchyma replacement by adipose tissue is incompletely understood, there are many factors which put one at increased risk. These include local factors, systemic factors, and syndromatic factors.

Local Factors

Pancreatitis is characterized by auto-digestion from inappropriately activated pancreatic enzymes and chronic pancreatitis is the most well known cause of pancreatic insufficiency [9]. Pancreatic ductal obstruction by gallstones, tumors, lipomas, sphincter of Odi spasm can all lead to increased ductal pressure and plugging with premature activation of enzymes, causing pancreatitis. Anatomic anomalies such as pancreatic divisum also cause pancreatitis. Chronic alcohol use can directly destroy pancreatic parenchyma without ductal plugging. Fat necrosis ensues after the destruction of acinar cells and can be seen on gross examination. Some evidence reveals inflammatory cytokines may promote fat deposition in non-adipose tissues such as the pancreas [10].

Lipomatous pseudohypertrophy is a pseudo-tumor formation by adipose tissue, replacing entire segments of exocrine pancreatic parenchyma. It is typically found incidentally on imaging, but can be worrisome due to its size and can be mistaken for a neoplastic process. Grossly, these tumors do have a mass effect on nearby pancreatic tissue. The etiology is unknown and can be distinguished from a lipoma by the absence of a surrounding capsule and the presence of atrophic pancreatic elements within the pseudo-tumor [11].

Pancreatic fat accumulation has also been induced in animal models by obstruction or ligation of the pancreatic duct or pancreatic vasculature. In a case series of 102 patients with pancreatic ductal adenocarcinoma (PDAC), there was a positive correlation with fatty infiltration of the pancreas, even after adjusting for BMI and DM [12]. However, it was uncertain if the PDAC was an effect of the fat infiltration or cause. The possible mechanism of ligation and/or obstruction of the pancreatic duct may be similar to that of pancreatitis and chronic inflammation. Decreasing vascular supply may cause death to the parenchyma, causing atrophy and adipose tissue replacement.

Systemic Factors

In obese patients, the term fat infiltration or pancreatic steatosis is more appropriate rather than fatty replacement due to the fact that this condition can be reversible upon weight reduction, much like non-alcoholic fatty liver disease [13]. Although the effects of metabolic syndrome on the exocrine pancreas are less well investigated than those on the liver, there are data in the literature which correlate obesity with pancreatic steatosis and its reversibility [14].

Pancreatic fatty replacement is the most common pattern seen in older adults with cystic fibrosis [15]. Patients with cystic fibrosis have a defective cystic fibrosis transmembrane conductance regulator (CFTR), which leads to impaired transport of chloride and sodium, and therefore water, causing viscous secretions into the exocrine pancreatic lumen [16]. As a result of proximal pancreatic duct plugging, when pancreatic enzymes are released into the lumen, chronic pancreatic inflammation ensues. Overtime, pancreatic parenchyma atrophies and is replaced by adipose tissue.

Primary and secondary hemochromatosis have been implicated as a cause of pancreatic lipomatosis. Pathologic examination of the pancreas in transfusion dependent patients has shown iron deposition in exocrine pancreatic cells, in addition to the Islets of Langerhan. When pancreatic cells die from the cytotoxic effects of iron, the atrophied pancreatic parenchyma is replaced by adipose tissue [17].

Steroid use and malnutrition have also been suggested as risk factors for development of pancreatic lipomatosis, but the pathyphysiology is unknown.

Syndromatic Factors

Shwachman Diamond syndrome (SDS) is an inherited bone marrow failure syndrome (IBMFS) characterized by exocrine pancreatic insufficiency, bone marrow dysfunction, and skeletal abnormalities. It is a defect in ribosomal maturation, and implicated in cell proliferation, mitosis, and maintenance of the stromal

microenvironment [18]. Imaging often reveals the characteristic fatty replacement of pancreatic parenchyma. Histological examination reveals fatty replacement of pancreatic acini while preserving islets of langerhans and ductal architecture [19]. In the case with our patient, fatty pancreas on imaging was the initial suspicion that led to further testing for SDS. Patients with SDS often present in infancy to early childhood with malabsorption and recurrent infections. However, they can present in adulthood with the first presentation being AML, in the case of our patient. Laboratory testing often reveals decrease in one or more cell lineage along with decreased pancreatic enzymes which often normalize with increasing age, the reason is not clear.

Johanson-Blizzard syndrome is another rare autosomal recessive multisystem disorder also characterized by fatty replacement of the exocrine pancreas. The mutation is in the UBR1 gene which encodes a ubiquitin ligase to degrade proteins at the proteasome for regulated protein degradation. UBR1 is considered to play a critical role in the development and maintenance of acinar cells. It can be distinguished from SDS by the lack of bone marrow manifestations and several clinical features absent in SDS.

The exocrine pancreas is the portion of the pancreas responsible for the release of digestive enzymes. Exocrine pancreatic insufficiency can result from fat accumulation or replacement in the exocrine pancreas, while insulin resistance can develop when fat accumulates or replaces the Islets of Langerhans. Unless there is complete fat replacement of the pancreas, pancreatic function remains relatively normal without clinically overt signs of insufficiency.

In conclusion, it is necessary for adult physicians to recognize SDS as a possible cause of pancreatic lipomatosis, particularly in patients who have cytopenia and hypoplastic bone marrow. Early diagnosis can allow patients to have proper management with less therapy-related adverse effects.

Conflicting of Interest

The authors had no conflicts of interest.

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