Pancreatic Sarcoidosis: A Literature Review

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ABSTRACT

Pancreatic involvement is a rare condition in the patients with systemic sarcoidosis. The incidence rate of pancreatic sarcoidosis is 1-6% of the patients with systemic disease. Symptoms related to pancreas involvement are not common and may vary from nonspecific abdominal pain or nausea and weight loss to a solid mass with obstructive jaundice. There is no specific diagnostic test for pancreatic sarcoidosis. It often is detected during surgery in the patients who are suspicious to malignant pancreatic mass and diagnosed by pathological evidences. However, Computed Tomography, magnetic resolution imaging and endoscopic ultrasound guided fine needle aspiration may be useful and safe modalities for differentiating malignant and benign pancreatic masses. There is no standard medical treatment for pancreatic sarcoidosis. Nevertheless, corticosteroid therapy may be considered for symptomatic patients. Generally, prognosis is good in the mild forms of disease and spontaneous remission rate is high.

BACKGROUND

Sarcoidosis that first was described by Hutchinson in 1877 is a chronic inflammatory disease without a definite etiology characterized by non caseous granulomas [1, 2, 3, 4]. The prevalence of this multisystemic disease is approximately 2-60 per 100000 persons and mostly affects young adults between 20-40 years. Women are affected more than men [5, 6]. Although it affects all races; however, higher rates of sarcoidosis has been reported amongst Afro-Americans, Scandinavians and Irish decent [1, 6, 7, 8]. Various risk factors such as environmental and genetic risk factors have been considered for sarcoidosis [7, 9, 10].

Although, it can involve almost any organs; but, pulmonary system is the most commonly affected site (90%) [6, 11]. Extra-thoracic involvement occurs in 30% of the patients [2, 12, ]. Isolated extra pulmonary sarcoidosis account for about 10% cases [13]. In some cases multiple organ involvement can present a difficult diagnosis, because they mimic metastatic cancer [14]. The most frequent extra-thoracic sites are abdomen with a frequency of 50-70%, liver with 50-80%, spleen with 40-80%, lymph nodes with 30% and kidney are the most common intra-abdominal sites of involvement in sarcoidosis [6, 15]. Eye involvement is reported in 25% of the patients with systemic sarcoidosis. Also, skin manifestations occur in 25% of cases with sarcoidosis [16]. The main cause of mortality in systemic sarcoidosis is due to cardiopulmonary involvement [6]. Generally a, mortality rate of 1-5% has been reported for sarcoidosis [17, 18].

Gastrointestinal involvement is rare in patients with systemic sarcoidosis and may be asymptomatic; so that in 60-90% of these cases, non-caseating granuloma was detected in liver biopsy [2, 16, 19]. Liver involvement in the absence of pulmonary disease is rare and has been reported in about 13% of cases with systemic sarcoidosis [2]. Although liver involvement is mainly asymptomatic; but, it can present with hepatosplenomegaly, elevated liver enzymes, intrahepatic cholestasis, portal hypertension, and cirrhosis [20].

The first report of pancreatic involvement in a patient with systemic sarcoidosis was published in 1937 by Nickerson. He found non-caseating granulomas in autopsy of pancreas in this patient [21, 22]. In 1950, Curran and Curran presented a case of pancreatic sarcoidosis with diffuse abdominal pain who was diagnosed via exploratory laparotomy [21, 23]. In 1963, Mayock reported three cases of pancreatic involvement amongst 287 patients with systemic sarcoidosis [24]. According to a large autopsy series in Japan, the frequency rate of 2.1% was reported for pancreatic sarcoidosis. Half of these cases were asymptomatic and died of other causes [21, 25]. Noguchi in 1993 reported 14 patients with pancreatic sarcoidosis. Six had swollen pancreas with diffused nodular changes, four had enlargement of the head, and only one patient had a combination of pancreatic head mass and diffuse...
Clinical Manifestations

Sarcoidosis is a multisystemic inflammatory disease of unknown origin. It is characterized by non-caseating epithelioid cell granulomas in the absence of other granulomatous diseases such as tuberculosis, fungal infections, autoimmune diseases, or delayed-type hypersensitivity reaction to foreign antigens [6, 23].

Diagnosis

Sarcoidosis is a multisystemic inflammatory disease of unknown origin. It is characterized by non-caseating epithelioid cell granulomas in the absence of other granulomatous diseases such as tuberculosis, fungal infections, autoimmune diseases, or delayed-type hypersensitivity reaction to foreign antigens [6, 23].

Laboratory tests to support the diagnosis include complete blood count (CBC), electrolytes, BUN/Cr, liver enzymes, alkaline phosphatase, calcium, urinalysis including urinary enzymes, alkaline phosphatase and immunoglobulins may be elevated. Hypercalcemia is defined as urinary calcium to creatinine ratio of more than 0.2 for normal patients over the age of two years with relatively normal body mass index. Men are more likely to have difficulties with calcium homeostasis than women and an elevated urinary calcium/Cr ratio thus more common than hypercalcemia. Elevated ACE is not diagnostic due to false-positives. However, it is found to be elevated in over 75% of cases of sarcoidosis lending further support to the diagnosis [58, 59].

Few case reports have mentioned laboratory results of pancreatic involvement in sarcoidosis. Nevertheless, laboratory findings are not specific for diagnosis of sarcoidosis. In a prospective study, 15 cases amongst 92 patients with sarcoidosis had an abnormal level of serum pancreatic amylase and 6 cases amongst 39 had an elevated serum immunoreactive trypsin. These findings suggest that clinical and subclinical abnormalities of pancreatic function are not uncommon in patients with sarcoidosis [60].

According to review literatures, pancreatic sarcoidosis can manifest as solid tumors; therfore, it may mimic pancreatic malignancies [33, 34, 36, 47, 49]. Varieties of differential diagnoses are considered for a pancreatic mass. For instance, pancreatic adenocarcinoma (PC), Primary pancreatic lymphoma (PPL), pancreatic neuroendocrine tumor (PNET), autoimmune pancreatitis (AIP), metastasis enlargement [21, 26]. In 2006, Caceres reported 25 patients with surgically proven pancreatic sarcoidosis of which 12 cases presented with a pancreatic mass localized to the head of pancreas, and 13 cases presented with a diffusely firm nodular pancreas [17, 21]. Pancreatic sarcoidosis rarely cause symptom and it appear diffuse nodular tissue infiltration, duct obstruction or peripancreatic lymphadenopathy or pancreatic head mass that should be differentiated from pancreatic adenocarcinoma [6]. Histologic finding of pancreatic sarcoidosis reveal non-casing granulomas with are also seen in other diseases including infectious autoimmune and neoplastic diseases [6, 13]. So that early diagnosis is warranted to avoiding unnecessary surgery [27].

In review of literatures within more than last 3 decades, we found more than 30 case reports of pancreatic sarcoidosis. In this review article we tried to summarize all about pancreatic sarcoidosis including clinical features, diagnostic methods, and treatment of this rare condition.

Clinical Manifestations

According to review literatures, incident rate of pancreatic involvement in the patients with systemic sarcoidosis is 1-6%. This involvement may be microscopic and found during autopsy as an incidental finding. In the other hand pancreatic sarcoidosis without involvement of other organs and with symptoms related only to the pancreas is extremely rare. In symptomatic cases, clinical presentations varies from nonspecific abdominal pain or acute pancreatitis with nausea and weight loss to a solid mass with obstructive jaundice. The acute symptoms were more common in younger patients (18 to 47 years) accompanied by variable hyperamylasaemia and calcaemia, while the chronic picture was more common in older age groups (25 to 67 years) suggesting the diagnosis of carcinoma. Women a slightly more than men may present with pancreatic mass. The most common site of pancreatic involvement is head of pancreas; while, involvement of tail or total pancreas is rare [1, 24, 27, 28].

In 25 cases with pancreatic sarcoidosis reported by Caceres in 2006 patients mostly presented with abdominal pain (66%), weight loss (49%), obstructive jaundice (29%) and emesis (20%), pruritus (12%), fever (8%), diarrhea (4%), abdominal distention (4%) and ascites (4%) [17, 30]. Three cases of pancreatic sarcoidosis presented as acute pancreatitis [28, 31]. Pancreatic symptoms are mostly due to pancreas infiltration or compression by enlarged lymph nodes [1]. Sarcoidosis may rarely present as a mass in the pancreas that mimics pancreatic cancers and need to surgery for confirming diagnosis [1, 6, 21, 27, 30, 32, 33, 34, 35, 36]. Furthermore, 16% of these patients reported a history of sarcoidosis; 35% had elevated amylase; 62% had elevated Angiotensin-converting enzyme (ACE) and 26% had bilateral hilar lymphadenopathy [17].

Up to 2006, 26 cases of pancreatic sarcoidosis had been reported and summarized by Caceres et al. [17]. By using key word of "pancreatic sarcoidosis" in PubMed and Scopus, we found another five cases since 2006 up to now. We add these patients to Caceres findings’ as following (Table 1):

Amongst these patients, there are 14 female and 17 male. Average age is 47. Head of pancreas was the most common site of involvement (in 15 cases).
Table 1. Summary of patients reported with pancreatic sarcoidosis.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Author</th>
<th>Age/Sex</th>
<th>Presentation</th>
<th>CXR</th>
<th>ACE</th>
<th>Amylase</th>
<th>Previous Sarcoi</th>
<th>Surgical Intervention</th>
<th>Surgical Findings</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Curran and Curran</td>
<td>48F</td>
<td>Nausea/vomiting, abd. pain, weight loss</td>
<td>Normal</td>
<td>N/A</td>
<td>Normal</td>
<td>No</td>
<td>Exploratory laparatomy, pancreatic biopsy</td>
<td>Firm, nodular pancreas</td>
<td>Diffuse</td>
</tr>
<tr>
<td>2</td>
<td>Ryrie</td>
<td>52F</td>
<td>Obstructive jaundice</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>Panc biopsy, biliary bypass</td>
<td>Mass in head of pancreas</td>
<td>Pancreatic head</td>
</tr>
<tr>
<td>3</td>
<td>Papowitz</td>
<td>28F</td>
<td>Abdominal distention</td>
<td>Normal</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>Exploratory laparatomy, splenectomy, distal pancreatectomy</td>
<td>Ascites, peritoneal granulomas, Nodular pancreas</td>
<td>Diffuse</td>
</tr>
<tr>
<td>4</td>
<td>Chaun</td>
<td>52M</td>
<td>Fever, abd pain, weight loss</td>
<td>Normal</td>
<td>N/A</td>
<td>Normal</td>
<td>No</td>
<td>Exploratory laparotomy, pancreatic biopsy</td>
<td>Enlarged, nodular pancreas</td>
<td>Diffuse</td>
</tr>
<tr>
<td>5</td>
<td>Caldwell</td>
<td>37M</td>
<td>Pruritis</td>
<td>Normal</td>
<td>N/A</td>
<td>126 IU/L</td>
<td>No</td>
<td>Cholecystectomy, com mon duct exploration</td>
<td>Firm, enlarged pancreas</td>
<td>Diffuse</td>
</tr>
<tr>
<td>6</td>
<td>Tsou</td>
<td>47F</td>
<td>Fatigue, weight loss, weakness</td>
<td>Elevated</td>
<td>Normal</td>
<td>Normal</td>
<td>Yes</td>
<td>Exploratory laparotomy for suspected uterine malignancy</td>
<td>Diffuse nodular pancreas</td>
<td>Diffuse</td>
</tr>
<tr>
<td>7</td>
<td>Maher</td>
<td>59M</td>
<td>Abdominal pain, nausea, weight loss</td>
<td>Normal</td>
<td>N/A</td>
<td>Normal</td>
<td>No</td>
<td>Exploratory laparotomy, transduodenal pancre biopsies</td>
<td>Diffusely enlarged pancreas</td>
<td>Diffuse</td>
</tr>
<tr>
<td>8</td>
<td>Friedman</td>
<td>48F</td>
<td>Weight loss, abdominal pain</td>
<td>Bilateral hilar enlargement</td>
<td>Elevated</td>
<td>68 IU/L</td>
<td>No</td>
<td>Exploratory laparotomy, pancreatic biopsy</td>
<td>Enlarged nodular pancreas, peripancreatic LN</td>
<td>Diffuse</td>
</tr>
<tr>
<td>9</td>
<td>Sagalow</td>
<td>25F</td>
<td>Acute abdominal pain</td>
<td>Normal</td>
<td>N/A</td>
<td>215 IU/L</td>
<td>No</td>
<td>Exploratory laparotomy, pancreatic biopsy</td>
<td>Enlarged pancreatic head, peripancreatic LN</td>
<td>Head of pancreas</td>
</tr>
<tr>
<td>10</td>
<td>Robaszewicz</td>
<td>30M</td>
<td>Abdominal pain</td>
<td>Reticulonodular pattern</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Yes</td>
<td>Exploratory laparotomy, pancreatic biopsy</td>
<td>Nodular pancreas, peripancreatic LN</td>
<td>Diffuse</td>
</tr>
<tr>
<td>11</td>
<td>Stampi</td>
<td>47M</td>
<td>Abdominal pain, emesis, weight loss</td>
<td>Mediastinal LN</td>
<td>N/A</td>
<td>1310 IU/L</td>
<td>Yes</td>
<td>Exploratory laparatomy pancreatic biopsies</td>
<td>Enlarged pancreatic head, peripancreatic LN</td>
<td>Head of pancreas</td>
</tr>
<tr>
<td>12</td>
<td>Brady et al.</td>
<td>67F</td>
<td>Abdominal pain</td>
<td>Normal</td>
<td>Normal</td>
<td>546 IU/L</td>
<td>No</td>
<td>Pancreatic-duodenectomy</td>
<td>Enlarged pancreatic head, peripancreatic LN</td>
<td>Head of pancreas</td>
</tr>
<tr>
<td>13</td>
<td>Toda</td>
<td>66M</td>
<td>Back pain, pruritus</td>
<td>Normal</td>
<td>Normal</td>
<td>Slight elevation</td>
<td>No</td>
<td>Exp lap, pancreatic biopsy</td>
<td>Enlarged pancreatic head, peripancreatic LN</td>
<td>Diffuse</td>
</tr>
<tr>
<td>14</td>
<td>Soyer</td>
<td>51F</td>
<td>Weight loss, abdominal pain, nausea, vomiting</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>Pancreatic biopsy choledocho and gastrojejunostomy</td>
<td>Enlarged nodular pancreas, peripancreatic LN</td>
<td>Head of pancreas</td>
</tr>
<tr>
<td>15</td>
<td>Espinoza-Aguilar</td>
<td>41F</td>
<td>Jaundice, pruritus</td>
<td>Normal</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>Peripancreatic node biopsy</td>
<td>peripancreatic lymphadenopathy</td>
<td>Head of pancreas</td>
</tr>
<tr>
<td>16</td>
<td>Garcia</td>
<td>52F</td>
<td>Anemia, splenomegaly</td>
<td>Hilar, mediastinal adenopathy</td>
<td>Elevated</td>
<td>Normal</td>
<td>No</td>
<td>Splenectomy, distal pancreatectomy</td>
<td>splenomegally</td>
<td>Diffuse</td>
</tr>
<tr>
<td>17</td>
<td>Garcia</td>
<td>34M</td>
<td>Severe abdominal pain</td>
<td>Bilateral hilar adenopathy</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>Exploratory laparatomy, peripancreatic node biopses</td>
<td>Nodular pancreatic tail, enlarged peripancreatic LN</td>
<td>Pancreatic tail</td>
</tr>
<tr>
<td>18</td>
<td>Garcia</td>
<td>33M</td>
<td>Fever, weight loss, abdominal pain</td>
<td>Bilateral hilar adenopathy</td>
<td>Elevated</td>
<td>N/A</td>
<td>No</td>
<td>Pancreatic, peripancreatic node biopses</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>19</td>
<td>Rodriguez</td>
<td>41F</td>
<td>Abdominal pain</td>
<td>Normal</td>
<td>N/A</td>
<td>Normal</td>
<td>No</td>
<td>Exp lap, pancreatic biopsies</td>
<td>Enlarged pancreatic head, peripancreatic LN</td>
<td>Head of pancreas</td>
</tr>
<tr>
<td>20</td>
<td>Snook</td>
<td>45M</td>
<td>Abdominal pain, diarrhea, weight loss, jaundice</td>
<td>Normal</td>
<td>N/A</td>
<td>Normal</td>
<td>Yes</td>
<td>Exp lap, pancreatic biopsy</td>
<td>Diffusely nodular pancreas</td>
<td>Diffuse</td>
</tr>
<tr>
<td>21</td>
<td>Siavelis et al.</td>
<td>61M</td>
<td>Obstructive jaundice, weight loss, jaundice</td>
<td>N/A</td>
<td>N/A</td>
<td>Normal</td>
<td>No</td>
<td>Pancreatic-duodenectomy</td>
<td>Pancreatic head mass</td>
<td>Head of pancreas</td>
</tr>
<tr>
<td>22</td>
<td>Bacal</td>
<td>54M</td>
<td>Jaundice</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>Pancreatic-duodenectomy</td>
<td>Pancreatic head mass</td>
<td>Head of pancreas</td>
</tr>
</tbody>
</table>

Table 1. Summary of patients reported with pancreatic sarcoidosis.
from other primary sites, and rare diseases such as pancreatic tuberculosis or pancreatic sarcoidosis. All of these conditions can mimic pancreatic adenocarcinoma [61]. Isolated metastatic cancers to the pancreas can be occur most commonly in melanoma, renal cell, lung, colon, gastric, breast, and ovarian cancers and rarely in prostate cancer [62, 63].

Although previous history of sarcoidosis can be helpful for diagnosing pancreatic involvement in a patients with pancreatic related signs and symptoms, but only 16% of patients mention history of systemic sarcoidosis before presenting symptoms that led to detection of pancreatic involvement [2].

So far, there is no specific diagnostic imaging for pancreatic sarcoidosis. Although CT is a useful modality for detecting pancreatic masses but it is not specific for diagnosing pancreatic sarcoidosis. Essentially, an ill-defined pancreatic head mass, narrowing and dilatation of the common bile duct with or without pancreatic duct dilatation, and enlarged lymph nodes are the most common CT findings reported in the literatures [1, 28, 33, 34, 64, 65, 66]. Figure 1 shows Computer tomography (CT) scan findings in a case of pancreatic sarcoidosis. It reveals a smooth shaped lesion involving the pancreatic head, measuring 3.6 cm at its greatest diameter [52].

Pancreatic sarcoidosis should be considered in the differential diagnosis of multiple pancreatic masses on MRI with low signal intensity on T1- weighted images, mild high signal intensity on T2- weighted images, and decreased enhancement compared to the normal pancreas after administration of gadolinium [64].

MRI findings in pancreatic sarcoidosis have been described in the literature in the last decade. For instance, in Baroni study, MRI findings of a patient with pancreatic sarcoidosis revealed multiple masses within the body and tail of the pancreas, with slight hyperintensity on T2-weighted images and delayed progressive enhancement after administration of gadolinium, becoming isointense to the rest of the pancreas on the portal venous and delayed venous phases (Figure 2) [64, 6]. Although, these findings are unusual in primary pancreatic adenocarcinoma, but some other differential diagnoses are strongly considered including

![Figure 1: Computer tomography (CT) scan findings in a patient with pancreatic sarcoidosis.](image-url)
non-hyperfunctioning neuroendocrine tumors, pancreatic metastases, lymphoma, and granulomatous infection [64].

Neuroendocrine tumors can be multiple and usually present as discrete nodules with low signal on T1-weighted images, and high signal on T2-weighted images. However, the majority of them will enhance to a greater degree than the normal pancreatic parenchyma during the arterial phase after administration of gadolinium [20]. Pancreatic metastases will present as multiple parenchymal masses in only 5–10% of cases, and their imaging aspects may resemble those of the distant primary neoplastic source (the most common being renal cell carcinoma) [25].

Endoscopic ultrasound (EUS) is a high sensitive and less aggressive modality for diagnosis small pancreatic tumors [67]. Several studies has compared CT, MRI and EUS for diagnosing, differentiating pancreatic mass. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is a safe procedure for diagnosing pancreatic mass with obtaining tissue samples for pathologic evaluation [68]. Fine-needle aspiration (FNA) cytology and fluid analysis together with morphological characteristics helps differentiate malignant lesions from benign masses [69]. The reported sensitivity and specificity of EUS-FNA for various solid lesions in pancreas are as high as 97% [70]. This modality is useful for differentiating other causes of pancreatic involvement such as pancreatic tuberculosis [71, 72, 73]. Thus, it may be a helpful procedure for diagnosing pancreatic sarcoidosis.

**Treatment**

So far, there is no standard medical treatment for pancreatic sarcoidosis. Although the prognosis is variable; but, the prognosis of mild pancreatic involvement is good, and spontaneous remission rate is high [2, 21, 48]. Generally, corticosteroids are drug of choice for treatment of sarcoidosis. It is recommended for management of more severe forms of sarcoidosis such as cardio pulmonary, ocular and central nervous system involvement as well as patients with malignant hypercalcemia and constitutional symptoms [21, 31, 75]. Corticosteroids control disease by suppressing the pro-inflammatory cytokines and chemokines involved in cell mediated immune response and granuloma formation [76].

There is no agreement on optimal dose and duration of corticosteroid therapy [76]. Long time corticosteroid therapy can be associated with complications such as hypertension, cushingoid effects, psychosis, osteoporosis, glaucoma, cataracts, hypokalemia, glucose intolerance, telangiectasis, acne, and gastropathy. Due to the serious effects of chronic corticosteroid pharmacotherapy, it should be used only after careful estimation of its risks and benefits. After discontinuing corticosteroids, the recurrence rate of pancreatic sarcoidosis in severe symptomatic cases is 100% [31].

It is proposed that corticosteroids may alleviate abdominal pain and reduce elevated serum level of amylase and lipase [77]. In the literatures, 18 patients...
with pancreatic sarcoidosis were followed up. Six patients improved without any treatment; whereas, 10 improved with corticosteroids [2, 17].

As alternative therapeutic methods, other non-steroidal drugs may be used in treatment of some refractory life-threatening forms of sarcoidosis such as azathioprin, methotrexate and hydroxyl chloroquine [4, 76, 78, 79]. In a case with pancreatic sarcoidosis presented with pancreatitis, mycophenolate mofetil was used successfully [80]. In recent years, numerous reports have been published about effectiveness of retuximab and infliximab in treatment of severe forms of sarcoidosis such as pulmonary and ocular sarcoidosis [79, 81, 82, 83, 84, 85].

**Conflicting Interest**

The authors had no conflicts of interest.

**References**
