Pancreatic Castleman's Disease: Studies of Three Cases And A Cumulative Review of the Literature

L. Fu · X. L. Wang · S. R. Babu · Y. Zhang · A. P. Su ·
Z. L. Wang · T. Hu · B. L. Tian

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Abstract Castleman's disease (CD) is a relatively rare and benign disorder. Pancreatic localization of CD is even more rare and is usually indistinguishable from pancreatic neoplasms. We report three cases of CD in which pancreas was all involved. One located in the tail of the pancreas, who accepted distal pancreatectomy, and the others in the head accepted enucleation. In addition, we review current data on its pathogenesis, imaging findings, diagnosis, differential diagnosis, and treatment.

Keywords Castleman's disease · Pancreas

Introduction

Castleman's disease (CD) is a relatively rare and benign disorder, characterized by giant lymph node hyperplasia. It was initially described as pathological entity in 1954 and later defined by Castleman in 1956 [1, 2]. Histopathologically CD presents with three distinct histological variants [3]. The hyaline vascular type (HV), also called angiofollicular lymphoid hyperplasia, is the most common histological variant of the CD. The second histological variant of CD is plasma cell type (PC), which is characterized by large lymphoid follicles

surrounded by sheets of plasma cells. The third histological variant of CD is mixed type (MV or HV-PC). Initially several articles reported that mediastinum followed by cervical region was the most common sites of disease. However, it can present in nonmediastinal sites wherever lymph nodes are present, and the common sites are the pelvic, retroperitoneum, and axillary regions. Pancreatic localization of CD is even more rare and is usually indistinguishable from pancreatic neoplasms. To our knowledge, only 19 cases of CD associated with pancreas were described in the world literature (Table 1) [4–22]. We report 3 cases of CD in which pancreas was all involved (Table 2). One located in the tail of the pancreas, who accepted distal pancreatectomy, and the others in the head accepted enucleation. In addition, we review current data on its pathogenesis, imaging findings, diagnosis, differential diagnosis, and treatment.

Case Report

Case 1

A 49-year-old man was admitted with a history of traffic accident for further investigation. He had no weight loss, change in appetite, bowel habits, jaundice, or general malaise. For a patient surveillance we prescribed him an abdominal ultrasound. Abdominal ultrasound demonstrated a well-defined mass in the tail of the pancreas. The abdominal computed tomography scan further confirmed a mass with punctiform calcification in the tail of the pancreas, measuring 4.5 cm×3.3 cm (Fig. 1). The tumor-associated antigen levels CA 19–9, CEA, and CA-125 were within the normal level. The physical examination and laboratory studies of the patient were absolutely normal. Our differential diagnosis still included adenocarcinoma of the pancreas. Our concern remained for possible undetected malignancy and diagnostic laparotomy

L Fu and XL Wang share first authorship in the article.

L. Fu
General Ward of Oncology, West China Hospital,
Sichuan University,
Chengdu 610041, Sichuan Province, China

X. L. Wang · S. R. Babu · Y. Zhang · A. P. Su · Z. L. Wang ·
T. Hu · B. L. Tian (✉)
Department of Hepatobiliopancreatic Surgery,
West China Hospital, Sichuan University,
Chengdu 610041, Sichuan Province, China
e-mail: jaanumithua@yahoo.com

Table 1 Summary of CD involving pancreas reported in the world literature

No	Author	Site	Symptoms	Pathologic type	Treatment	Recurrence
1	Goetze [4]	Tail	No	HV	DP	NER(2 yrs)
2	Erkan [5]	Peripancreatic	Abdominal pain	PC	Enucleation	NER(1 yr)
3	Baikovas [6]	Peripancreatic	No	HV	Excision	NA
4	Lepke [7]	Body and tail	No	HV	STP	NA
5	Corbisier [8]	Peripancreatic	Abdominal pain	HV	Excision	NA
6	LeVan [9]	Tail	Back pain	HV	DP	NA
7	LeBorgne [10]	Head	Systemic	PC	PD	NER(11mos)
8	Brossard [11]	Tail	Systemic	PC	DP	NA
9	Wang [12]	Head	No	HV	PD	NER(1 yr)
10	Justyna [13]	Head	Abdominal pain	HV-PC	Partial excision	Died(137ds)
11	Maithel [14]	Head	Systemic,jaundice	PC	Laparotomy	NA
12	Yilmaz [15]	Head	Fatigue	HV	PD	NA
13	Chaulin [16]	Body and Tail	Fever	HV-PC	Excision	NA
14	Charalabopoulos [17]	Body	Epigastric pain	PC	DP	NER(2 yrs)
15	Rhee [18]	Body	No	HV	Excision(laparoscopic	NER(until published)
16	Tunru-Dinh [19]	Body and tail	Abdominal pain	HV	DP	NER(1 yr)
17	Mangini [20]	Body	Abdominal pain	HV	Excision	NA
18	Soler [21]	Body and tail	No	PC	DP	NA
19	Campira [22]	Head	No	PC	Excision	NA

HV hyaline-vascular type; *PC* plasma cell type; *HV-PC* hyaline-vascular plasma cell mixed type; *DP* distal pancreatectomy; *STP* subtotal pancreatectomy; *PD* Pancreaticoduodenectomy; *NED* no evidence of recurrence; *NA* not available

performed. Laparotomy confined the mass located in the tail of the pancreas without distorting the surrounding tissue. He was performed resection of the body and tail of the pancreas including spleen (distal pancreatectomy), and regional lymph nodes were identified. Postoperative microscopic examination revealed a giant lymph node hyperplasia (Castleman's disease) of hyaline vascular type (Figs. 2). The patient recovered well following the procedure and was discharged on the seventh postoperative day. Meanwhile, he continued to receive close outpatient surveillance for 10 months without any additional treatment and recurrence.

Case 2

A 39-year-old man who had experienced a mild intermittent, nonradiating upper abdominal pain of 6-month duration was admitted to our department. He had no any other history

with normal temperature, no night sweats, no fatigue, no change in appetite, normal bowel habits, no jaundice, no generalized malaise, and no significant change in body weight. Past surgical history included appendectomy about 12 years ago. His physical examination and laboratory findings, including tumor markers and inflammatory mediators, revealed nothing in particular with no any superficial lymph node enlargement. The CT scan revealed a cystic mass located at pancreatic head, measuring 5 cm×3.5 cm in size, with normal pancreatic duct, and adjacent decomposition was more clearly seen. However, it showed the multiline neoplastic lesion with a retroperitoneal source, as well might be a exogenous pancreatic carcinoma. Preoperative routine examination and tumor markers had no significant abnormalities. The initial diagnosis was adenocarcinoma of pancreatic head, and the patient underwent a local enucleation of the tumour. During surgery, a solid and cystic mass was found in the head

Table 2 Data of current cases

Case	Gender	Age(yr)	Symptoms	Site	Size(cm)	Treatment	Pathologic type	Recurrence
Case1	M	49	No	Tail	4.5×3.3	DP	HV	NED (10 mnth)
Case2	M	35	Abdominal pain	Head	5.0×3.5	Enucleation	undecided	NA
Case3	M	74	micturation	Head	3.0×2.4	Enucleation	PC	NED (26 mnth)

DP distal pancreatectomy; *HV* hyaline-vascular type; *PC* plasma cell type; *NED* no evidence of recurrence; *NA* not available

Fig. 1 CT scan: a solid neoplasm with punctiform calcification localized in the tail of the pancreas

of the Pancreas with palpated lymph nodes. Hence we performed local enucleation of tumour with regional lymph nodes cleared for him. Histopathological examination showed giant lymph node hyperplasia (Castleman's disease) of undecided type. He made an uneventful postoperatively recovery but failed to be followed-up.

Case 3

A 74-year-old man was admitted with complaint of difficulty in micturition for 1 month. He denied abdominal pain and other symptoms. On admission, physical examination noted with normal vitals signs and there were no stigmata of medical or surgical renal disease. He underwent MRI scan suggestive of mass in the pancreatic head with 3 cm × 2.4 cm in diameter. Pancreatic duct was normal. Preoperative routine examinations and tumor markers had no significant abnormalities. Still

Fig. 2 Microscopy revealed obvious hyperplasia in germinal center, with characteristic onion-skin appearance of the hyaline vascular type (hematoxylin and eosin, X 200)

pancreatic adenocarcinoma was suspected and exploratory laparotomy was performed. Laparotomy confirmed the mass located at the head superior of the pancreas with mild fundal adhesion. Enucleation of tumor was performed. Histological analysis revealed CD of the plasma cell type. The patient recovered well and was discharged with advice to receive close outpatient surveillance. The patient had been on monitoring on the outpatient basis for 26 months without any additional treatment and recurrence.

Discussion

Castleman's disease is a rare noncancerous disorder that causes cells in the lymph node to grow uncontrollably. CD is not officially a cancer but the multicentric form of disease acts very much like lymphoma. In fact, many people with this disease eventually develop lymphomas [23–26]. That is why it is also included in American Cancer Society's *World Journal of Surgical Oncology*. A variety of terms, such as angiofollicular lymph node hyperplasia, angiomatous lymphoid, Castleman tumor, giant benign lymphoma, hamartoma of lymphatics, and giant lymph node hyperplasia, are used to describe this disorder, and it is possible that the main title of the report CD is not the name you expected. CD affects children as well as adults, and no significant sex predilection has been found, regardless of the histological type. Younger people are more likely to have the localized form. Older adults and those with HIV infection are more likely to have the multicentric form. Till yet there is no consensus on underlying etiology of CD, but two theories have been put forward. One theory submits that the disorder represents a reactive lymphoid hyperplasia, initiated by chronic antigenic stimulation associated with a viral trigger (which remains undefined). The other one proposes that the masses are due to a developmental growth disturbance of the lymphoid tissue (i.e., a vascular lymphoid hamartoma). Several other factors are said to be related to CD in which the HIV and human herpes virus 8 (HHV-8) infection leads to oversecretion of IL-6, adhesion molecule, follicular dendritic cell dysplasia, etc. In addition CD has been also been associated with very high incidence of autoimmune phenomena such as autoimmune cytopenias, peripheral neuropathy, and systemic lupus erythematosus. Clinically two main forms of CD have been reported. Localized Castleman's disease (LCD) only affects a single set of lymph nodes. It is not widespread. The lymph nodes in the chest and abdomen are affected most often. The other clinical form is multicentric Castleman's disease (MCD) which always affects more than single group of lymph nodes. MCD is more serious than the localized form, particularly in people with HIV infection.

Histopathologically, CD presents with three distinct histological variants. The HV type usually presents as asymptomatic and is rarely associated with systemic disease; therefore, the true diagnosis of a CD was significantly delayed in most cases because of low index of the suspicion of the possibility of HV type of CD. The second histological variant of CD was plasma cell type (PC) characterized by large lymphoid follicles surrounded by sheets of plasma cells. The PC variant can be much more severe than the HV form and has a strong association with extrathoracic, multicentric, and highly aggressive disease. The systemic manifestation associated with the PC variant consists of fever, cytopenias, organomegaly, polyclonal hypergammaglobulinemia, and elevated erythrocyte sedimentation rate (ESR) as well as renal and hepatic dysfunction. The third histological variant of CD was mixed type (MV). The MV type gives a mixed variety of symptoms in which variants can only be distinguished after biopsy. There were 10 cases of HV type, 7 PC type, and only 2 mixed type among the reported 19 cases.

The initial challenge in CD remains in establishing the diagnosis and differentiating the disease mimicking CD which includes infectious and inflammatory lesions such as lymphadenitis, tuberculosis, sarcoidosis, toxoplasmosis, cytomegalovirus, infectious mononucleosis, and CD disease involving the pancreas from pancreatic carcinoma. The radiological differential diagnosis includes various neoplastic such as neurofibroma, cervical lipoma, Hodgkin's disease, thymoma, and lymph node metastasis. The diagnosis of CD is ultimately by histology, thereby requiring either removal or biopsy of the lesion for definitive diagnosis, in which HV type is characterized by extensive capillary proliferation and lymphocyte—predominant infiltrate surrounding germinal centers. The PC type has sheets of mature plasma within the interfollicular tissues surrounding larger germinal centers and has significantly less vascularity. Interestingly, all 19 cases yet reported were the consideration of pancreatic or peripancreatic neoplasia or lymphoma preoperatively, including the one in which Rhee et al. [18] tried the first endoscopic ultrasonography (EUS)-guided trucut biopsy for diagnostic modality from peripancreatic lesions.

The immunohistologic and immunologic gene rearrangement studies of the specimens can be useful in solidifying the diagnosis which resembling CD. Identifying an immunophenotypically varied population of B lymphocytes with polyclonal surface and cytoplasmic immunoglobulin markers helps to confirm the diagnosis of CD and differentiate it from lymphoma. In addition, CT scan, USG, and MRI imaging have been proved to be beneficial in diagnosing and establishing differentiation whether it is localized or

multicentric CD. It is also beneficial in diagnosing retroperitoneal tumors. In CT scan features may present as an isolated smoothly margined pancreatic mass that is well-circumscribed which may or may not invade main pancreatic duct and pancreatic parenchyma. However, CD is indistinguishable radiologically by other disease and the diagnosis ultimately rests on precise pathologic investigation.

Reviewing the three cases involving the pancreas in our hospital, we found that they all were clinically LCD forms. Their CT scans showed as round and well-defined mass—in one case involving the tail of the pancreas and in two cases invading the head of the pancreas. The mass was isointense with the pancreatic parenchyma without any clear border separating it from the normal parenchyma. The mass was homogenous in density with a punctuate calcification present at center with normal pancreatic duct. Treatment mainly depended on the presentation, clinical variant, and the location. However for LCD, surgical excision is the mainstay or treatment of choice associated with the best chance of cure. The treatment for MCD has not been established due to its variable clinical course and presentation, and surgery may play a limited role for palliation of systemic symptoms. Corticosteroids, immunotherapy, antimitotics, and radiotherapy may play a role to control systemic symptoms and prolong life. Drugs such as melphalan and tocilizumab may be useful. The worst prognosis of MCD is with the signs of neuropathy and renal failure. Radiotherapy has been used with success in patients who are poor candidates of surgical intervention and those with unresectable lesions and immunocompromised patients. Frequent follow-up is very important for these patients.

Conclusion

CD is a poorly understood disease that creates both the therapeutic and diagnostic dilemmas for surgeons. Till now, several articles, reviews, and case reports on CD involving its common site have been published, but only 19 cases have been published in world literature involving pancreas. Clinicians should be aware that CD may involve in pancreatic tissue which lead to difficulties in arriving at a differential diagnosis. It may present as asymptomatic or manifest as a systemic condition which makes a dilemma for the surgeons. Histopathological examination after complete resection of tumor or a resection of a part of mass gives a definitive diagnosis of CD. An early diagnosis, understanding of the pathogenesis, and natural history of the disease may lead to improvement over the current modalities available for treatment.

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