Abstract

Background: Castleman's disease of the pancreas is a very rare condition that may resemble more common disease entities as well as pancreatic cancer.

Case presentation: Here we report the case of a 58-year-old African American male with an incidentally discovered lesion in the head of the pancreas. The specimen from his pancreaticoduodenectomy contained a protuberant, encapsulated mass, exhibiting microscopic features most consistent with localized/unicentric Castleman’s disease. These included florid follicular hyperplasia with mantle/marginal zone hyperplasia along with focal progressive transformation of germinal centers admixed with involuted germinal centers.

Conclusion: To date, eight cases of Castleman's disease associated with the pancreas have been described in the world literature. We report the first case of unicentric disease situated within the head of the pancreas. In addition, we discuss the diagnostic dilemma Castleman’s disease may present to the pancreatic surgeon and review current data on pathogenesis, treatment, and outcome.

Background

Localized lymphoid hyperplasia of the pancreas is rarely reported and is often indistinguishable from pancreatic neoplasms both clinically or radiographically [1,2]. Castleman's disease (CD), a morphologically distinct form of lymph node hyperplasia is very rare, and even more infrequent in the pancreas [3]. Currently, there are only eight reported cases in the literature [3-10]. In our case, the lesion within the head of the pancreas was presumed to be a pancreatic carcinoma, and a classical pancreaticoduodenectomy (PD) was performed. Pathological examination instead revealed changes consistent with a localized or unicentric hyaline-vascular (HV) variant of CD within the head of the pancreas. In this communication, we
review the diagnosis, pathogenesis, treatment, and outcome for this rare clinical entity.

**Case presentation**

A 58-year-old African American male was seen in hepatology clinic for a surveillance liver ultrasound following a diagnosis of hepatitis C. The patient had experienced mild intermittent upper abdominal pain consistent with a history of gastroesophageal reflux disease. He had no weight loss, change in appetite or bowel habits, jaundice, or general malaise. Past medical history included hyperlipidemia, peptic ulcer disease, and hepatitis C (antibody positive, PCR negative). The patient's physical examination and laboratory studies were otherwise normal. A surveillance abdominal ultrasound demonstrated a well-circumscribed mass measuring 3.4 × 2.9 cm within the head of the pancreas. A computed tomography (CT scan) further confirmed an enhancing mass involving the head of the pancreas (Figure 1). No evidence of extra-pancreatic disease was found on further evaluation. Although tumor-associated antigen levels (CEA, CA 19-9, and CA-125) were normal our differential diagnosis still included adenocarcinoma of the pancreas. Endoscopic ultrasound (EUS) guided needle biopsy was then performed but the pathological findings were non-diagnostic. Our concern for possible undetected malignancy remained and a diagnostic laparoscopy was performed followed by PD. The patient recovered well following the procedure and was discharged home on the 15th postoperative day. He continues to receive close outpatient surveillance without additional treatment.

**Pathologic findings**

Within the PD specimen, a protuberant 4 × 3 × 3 cm circumferential mass at the superior border of the pancreatic head was appreciated (Figure 2). The external surface of the mass was tan/gray, firm, and smooth. Cut sections of the mass also revealed a partially encapsulated large nodule with tan/gray fleshy to firm parenchyma infiltrating the pancreas at its distal portion. Surgical margins were clear (Figure 3). Regional lymph nodes were identified near the mass; microscopic examination revealed that all were hyperplastic lymph nodes. The remaining surgical margins were negative.

This lymphoid lesion within the pancreatic head showed marked vascular proliferation and hyalinization of germinal centers. Involved germinal centers were surrounded by concentric rings of small lymphocytes, i.e. “onion-skinning” penetrated by hyalinized vessels (Figure 4). Moreover, the interfollicular zones were rich in plasma cells and hyalinized vasculature. These features are consistent with localized hyaline-vascular type CD. Distribution of T and B cell markers (CD20, CD3, CD45) was normal and markers indicative of lymphoid malignancies (i.e. CD30, CD15, CD5, CD10, BCL-2) did not show evidence of such entities. Furthermore, PCR analysis of paraffin-embedded tissue revealed no clonal rearrangement of the immunoglobulin heavy chain or T-cell receptor gamma and beta chain genes. *MALT1* (18q21) clonal rearrangement by FISH was negative. Together, these morphologic and immunohistochemical findings are most consistent with a diagnosis of CD.
Discussion

Historically, CD, also known as angiofollicular lymph node hyperplasia, remains a rare and poorly understood disease characterized by massive growth of lymphoid tissue. CD was first described as a pathological entity in 1954 and later defined by Castleman et al., in 1956 [11]. A variety of terms have been used to describe this disorder, including giant lymph node hyperplasia, lymph node hamartoma, follicular lymphoreticuloma, benign giant lymphoma, angiomatous lymphoid hamartoma, and angiofollicular mediastinal lymph node hyperplasia. Flendrig and Schillings [12] described two basic histopathological subtypes and one mixed variant which Keller et al. [13] later designated HV, plasma cell (PC), and hyaline-vascular plasma cell “mixed” types (HV-PC). Categorization of CD into clinically relevant subtypes was proposed by McCarty et al. [14] and Gaba et al. [15] into unicentric and multicentric variants, respectively. In general, HV-CD is commonly associated with a localized - asymptomatic mass (76–91%) [15,16], while PC-CD is usually multicentric and symptomatic in 50% of patients.

Unicentric and multicentric CD differ in their clinical presentation and distribution of adenopathy. In a series from Memorial Sloan-Kettering Cancer Center (MSKCC) [16], patients with unicentric CD were frequently discovered incidentally with symptoms mostly arising from mass compression. Masses found in unicentric disease were usually centrally located in the abdomen and pelvis (54%) and mediastinum (31%), whereby systemic symptoms, central and peripheral adenopathy, organomegaly, and associated abnormal laboratory values (elevated erythrocyte sedimentation rates [ESR], interleukin-6 [IL-6], anemia and polyclonal gammaglobulinemia) were predominant in the multicentric variant.

Our current understanding of the pathogenesis of CD points to reactive follicular hyperplasia in response to an unknown antigenic stimulus [17]. In the current report, the role of HCV infection (positive serology for anti-HCV) in the pathogenesis of HV-CD is possible. This view has been shared by others. Multicentric PC-CD has been previously reported to be associated with concurrent HCV infection in a child with Klinefelter’s syndrome and non-regulated antibody production mimicking systemic lupus erythematosus stabilized by interferon-alpha therapy suggesting an association with HCV [18]. Likewise, a report associating reactive lymphoid hyperplasia representing a pseudo-lymphoma of the liver was detailed in a patient with chronic hepatitis C [19]. Moreover, the potential role of HCV infection in an antigen-driven lymphoproliferative model for the pathogenesis of unrelated lymphoproliferative disease entities including non-Hodgkin’s lymphoma, marginal zone B-cell lymphoma, or extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) further supports this hypothesis. Nevertheless, the association of concurrent HCV infection and HV-CD requires further investigation. In addition, other etiologies including chronic low grade inflammation [11], harmartomatous process [20,21], immunodeficiency [22-24], and autoimmunity [25] have all been proposed as possible pathogenic mechanisms. Epstein-Barr virus, Toxoplasma, and Mycobacterium tuberculosis also have been linked to this disorder [13,25]. Interestingly, lymph nodes from various animal models and patients with CD implicate IL-6 as a causative agent for the commonly observed systemic manifestations [20,26-29].

The initial challenge in CD remains in establishing the diagnosis. Considerable imprecision exists in distinguishing CD from other lymphoid and non-lymphoproliferative disorders that it may resemble clinically and pathologically [30]. Therefore, in the appropriate clinical setting, the diagnosis of CD must be considered, after investigating and excluding more common causes of lymphadenopathy or associated neoplastic processes. Intraoperatively, distinguishing CD involving the head of the pancreas from pancreatic carcinoma may be problematic and strong suspicion of pancreatic malignancy as in our case may prompt traditional surgical removal. Possible clues for the pancreatic surgeon may include evidence of an encapsulated pancreatic mass that is well-circumscribed, and smooth; an uncommon finding for pancreatic adenocarcinoma. Indeed, the diagnosis ultimately rests on precise pathologic investigation.
Unicentric CD is largely the HV-type. HV-CD typically occurs as an isolated lymph node mass or regional adenopathy. These patients are frequently asymptomatic. From a histopathologic standpoint, "lollipop" follicles; germinal centers surrounded by circumferentially arranged layers ("onion skin") of small lymphocytes interconnected by a prominent vascular stroma are characteristic pathological findings. In this report, our patient had all the classical features of unicentric HV-CD. Conversely, the PC-CD subtype demonstrates continuous sheets of dense plasma cells and a less vascular interfollicular stroma surrounding the germinal centers [13].

Unicentric CD specifically involving the pancreas is extremely rare, with only eight cases described worldwide [3-10] (Table 1). The majority of these cases were of the HV-subtype and discovered incidentally. The PC-subtype typically presents with systemic symptoms. In those cases with patient follow-up it appears that resection may offer short-term control of disease with resolution of associated symptomatology.

Additional studies have further clarified the natural history following resection. From a consensus standpoint, surgical resection is the mainstay of treatment for unicentric CD with most reports describing complete resection as being curative. In a recent report from MSKCC [16], complete resection of unicentric disease was curative for all patients regardless of histologic subtype. Likewise, Keller et al. [13] retrospectively examined 61 patients with unicentric disease who were treated with surgery over a 20 year period. Their study demonstrated that for patients with unicentric HV-CD, complete resection offered the best chance for cure. In certain cases, if complete resection is not possible, partial resection or observation with long term follow-up may be useful. As reported, radiographic examination (CT or MRI) along with arteriography and embolization has been used to facilitate surgical excision and minimize intraoperative bleeding, which can be profuse [31-34].

A limited number of reports address the response of CD to radiotherapy (2700–4500 cGy) administered to involved sites which has resulted in remission of disease in isolated cases [28,35-42], but failed in others [13,15,43]. Keller et al. [13], reported on four patients with unicentric-HV disease who were treated with 1800–4300 cGy with no response. Notably, a complete response of the unicentric-HV variant was reported by Sethi et al. [40], in a patient with systemic symptoms treated with 4000 cGy. However, irradiation was noted to produce a range of favorable responses in all patients of PC or mixed histology [35,36,38,39,42]. These results point to a better

Table 1: Summary of patients with unicentric Castleman’s disease involving the pancreas

| Author       | Site            | Symptoms        | Subtype     | Treatment | Outcome       |
|--------------|-----------------|-----------------|-------------|-----------|---------------|
| Goetze³      | Tail of Pancreas| No              | HV-CD       | DP        | NED (2 Yrs)   |
| Erkan⁴       | Peripancreatic  | Abdominal pain*| PC-CD       | Enucleation| NED (1 yr)   |
| Baikovas⁵    | Peripancreatic  | No              | HV-CD       | Excision  | NA            |
| Lepke⁶       | Body and Tail   | No              | HV-CD       | STP       | NA            |
| Corbisier⁷   | Peripancreatic  | Abdominal pain  | HV-CD       | Excision  | NA            |
| LeVan⁸       | Tail of Pancreas| Back pain       | HV-CD       | DP        | NA            |
| LeBorgne⁹    | Uncinate Process| Systemic       | PC-CD       | PD        | NED+ (11 mos) |
| Brossard¹⁰   | Tail of Pancreas| Systemic       | PC-CD       | DP        | +             |
| Current Report| Head of Pancreas| No              | HV-CD       | PD        | NED (1 yr)   |

HV-CD: hyaline vascular Castleman’s disease; PC-CD: plasma cell Castleman’s disease; * Elevated erythrocyte sedimentation rate, C-reactive protein, and hypergammaglobulinemia; DP: distal pancreatectomy; STP: subtotal pancreatectomy; PD: pancreaticoduodenectomy; + resolution of systemic symptoms; NED: No evidence of disease; NA: Not available
response when radiotherapy is administered at an earlier, more active stage of disease (PC and mixed- HV-PC unicentric subtypes), rather than with the later, less metabolically active HV-subtype.

Subsequently, close follow-up and periodic surveillance are necessary to detect concurrent or ensuing malignant lesions (lymphoproliferative disease and vascular neoplasms) [44,45] associated with CD. Notably, local recurrence has been reported as long as 11 years after complete resection.

In contrast, no effective therapy has been established for multicentric disease which is widely viewed as a systemic disease. Among very rare cases, surgery may play a limited role for cases of palliation of systemic symptoms. Steroids, single-agents, or combination chemotherapy, plus immunotherapy are currently being employed with results ranging from rare cases of complete remission, sustained manifestations of disease, to aggressive disease biology with rapidly fatal outcomes [43,46,47]. The worst prognosis is for patients with multicentric disease, PC-subtype, and clinical signs of neuropathy. This group appears refractory to all therapy [46]. Long term survival may be possible in multicentric patients harboring the HV-subtype.

In this report, our patient underwent a PD for a presumed pancreatic cancer. In most cases, surgeons who treat pancreatic cancer will usually proceed to surgery without biopsy if the evidence of malignancy is strong. In this case, the initial biopsy did not demonstrate cancer. However, a study that is negative for tumor should not always be interpreted as meaning that no tumor exists. In this instance, a curable form of CD was resected. Due to the rarity of this disease, a diagnosis of CD will usually occur well after pathologic exclusion of other more common disease entities.

Conclusion

CD is a poorly understood disease that creates both a diagnostic and therapeutic dilemma for surgeons. Complete surgical resection of unicentric disease at the time of presentation is likely to afford the best chance for cure. Radiation therapy has been used with varied success in patients who are poor surgical candidates or in those with unresectable lesions. Long term follow-up is necessary with regard to malignant sequelae. The role of surgery in multicentric disease is limited and should not be considered a realistic treatment option. Systemic therapy in the form of steroids, single or multiple drug chemotherapies have all been used with varied success. However, there is no evidence for one approach being more consistently effective. A better understanding of the pathogenesis, natural history, and ultimately diagnosis of this disorder may lead to improvement over the current modalities available for treatment.

Competing interests

The author(s) declare that they have no competing interests.

Authors’ contributions

HW-Drafting manuscript, acquisition of data, RLW-acquisition of data, analysis and interpretation, MEZ-revising of manuscript, FDL-acquisition of data, analysis and interpretation, BCG-revising of manuscript, WBB-drafting of manuscript, analysis and interpretation, revising manuscript.

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Written consent of patient was obtained for publication of this case report.

References

1. Hatzitheoklitos E, Buchler MW, Friess H, Freiss H, DiSebastiano P, Poch B, Beger HG, Mohr W: Pseudolymphoma of the pancreas mimicking cancer. Pancreas 1994, 9:668-670.
2. Nakashiro H, Tokunaga O, Watanabe T, Ishibashi K, Kuwaki T: Localized lymphoid hyperplasia (pseudolymphoma) of the pancreas presenting with obstructive jaundice. Hum Pathol 1991, 22:724-726.
3. Goetze O, Banasch M, Junker K, Schmidt WE, Szymanski C: Unicentric Castleman’s disease of the pancreas with massive central calcification. World J Gastroenterol 2005, 11:6725-6727.
4. Erkan N, Yildirim M, Solek E, Sayhan S: Peripancreatic Castleman disease. J Pathol 2004, 204:491-494.
5. Baikovas S, Glenn D, Stanton A, Vonthethoff L, Morris DL: Castleman’s disease: An unusual cause of a peripancreatic hiliar mass. Aust N Z Surg 1994, 64:219-221.
6. Lepke RA, Pagani JJ: Pancreatic Castleman disease simulating pancreatic carcinoma on computed tomograph. J Comp Assisted Tomography 1982, 6:1193-1195.
7. Corbissier F, Ollier JC, Adloff M: Pancreatic localization of a Castlemans tumor. Acta Chir Belg 1993, 93:227-239.
8. LeVan T, Clifford S, Staren ED: Castleman’s tumor masquerading as a pancreatic neoplasm. Surgery 1989, 106:884-887.
9. Le Borgne J, Joubert M, Emam N, Gaillard F, Lafergue JP, Moussu P, Lebrun PA: Pancreatic localization of a Castleman’s tumor. Gastroenterol Clin Biol 1999, 23:536-538.
10. Brossard G, Ollier S, Pellegrin JL, Barbeau P, De Mascarel A, Leng B: Pancreatic Castleman’s tumor revealed by prolonged fever. Presse Med 1992, 21:86.
11. Castelman B, Ierson L, Menendez VP: Localized Mediastinal Lymph-Node Hyperplasia Resembling Thymoma. Cancer 1956, 9:822-830.
12. Fiendrig JA: Benign giant lymphoma: clinicopathologic correlation study. In The year book of cancer Edited by: Clark RL, Cumley RW, Year Book Medical Publishers; 1970:296-99.
13. Keller AR, Hoehholzer L, Castleman B: Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 1972, 29:670-83.
14. McCarty MJ, Vukelja SJ, Banks PM, Weiss RB: Angiofollicular lymph node hyperplasia (Castleman's Disease). Cancer Treat Rev 1985, 12:291-298.

15. Gaba AR, Stein RS, Sweet DL, Varakjis DJ: Multicentric giant lymph node hyperplasia. Am J Clin Pathol 1978, 69:86-90.

16. Bowne WB, Lewis JJ, Filippa DA, Nieszivisky R, Brooks AD, Burt ME, Brennan MF: The management of unicentric and multicentric Castleman's disease: a report of 16 cases and a review of the literature. Cancer 1999, 85:706-717.

17. Kojima M, Nakamura S, Miyawaki S, Ohno Y, Sakela N, Majawa N: Progressive transformation of germinal center presenting with histologic features of hyaline-vascular type of Castleman's disease. APMIS 2005, 113:288-295.

18. Simko R, Nagy K, Lombay B, Kiss A, Minik K, Lukacs VH, Vamosi I: Multicentric Castleman disease and systemic lupus erythematosus phenotype in a boy with Klinefelter syndrome: long-term disease stabilization with interferon therapy. J Pediatr 1993, 123:180-183.

19. Kim SR, Hayashi Y, Kang KB, Soe CG, Kim JH, Yang MK, Itoh H: A case of pseudolymphoma of the liver with chronic hepatitis. J Hepatol 1997, 26:209-214.

20. Hsu S-M, Waldron JA, Xie S-S, Barlogie B: Expression of interleukin-6 in Castleman's disease. Hum Pathol 1993, 24:833-839.

21. Tung KSK, McCormack LJ: Angiomatosus Lymphomatoid Hamartoma. Report of Five Cases with Review of the Literature. Am J Surg Pathol 1984, 8:13-21.

22. Lachant NA, Sun Nora CJ, Leong LA, Oseas RS, Prince HE: Multicentric Angiofollicular Lymph Node Hyperplasia (Castleman's Disease) Followed by Kaposis Sarcoma in Two Homosexual Males with Acquired Immunodeficiency Syndrome (AIDS). Am J Clin Pathol 1985, 83:27-33.

23. Okesnendler E, Duarte M, Soulier J, Cacoub P, Welker Y, Cadranel J, Cuzals-Hatem P, Autran B, Clauvel JP, Raphael M: Multicentric Castleman's disease in HIV infection: a clinical and pathologic study of 20 patient. AIDS 1996, 10:61-67.

24. Frizzera G: Castleman's Disease: More Questions than Answers. Hum Pathol 1985, 16:202-205.

25. Leith M: Interleukin-6. Clin Invest 1993, 11:732-742.

26. Yoshizaki K, Matsuda T, Nishimoto N, Kuritani T, Taeho L, Aozasa K, Nakahata T, Kawai H, Tagoh H, Komori T: Pathogenic significance of Interleukin-6 (IL-6/BSF-2) in Castleman's Disease. Blood 1989, 74:1360-1367.

27. Leger-Ravet MB, Peuchmaur M, Devergne O, Audouin J, Raphael M: The expression of interleukin-6 antibody. J Exp Med 1994, 179:602-605.

28. Weisenburger DD, Nathwani BN, Winberg CD, Rappaport H: Multicentric Angiofollicular Lymph Node Hyperplasia: A Clinicopathologic Study of 16 Cases. Hum Pathol 1985, 16:162-172.

29. Fitzpatrick PJ, Brown TC: Angiofollicular Lymph Node Hyperplasia. CMAJ 1997, 99:1259-1262.

30. Marti S, Pahissa A, Guardia J, Moragas A, Bacardi R: Multicentric giant follicular lymph node hyperplasia: A favorable response to radiotherapy. Cancer 1983, 51:808-810.

31. Stokes SH, Griffith RC, Thomas PRM: Angiofollicular lymph node hyperplasia (Castleman's Disease) associated with vertebral destruction. Cancer 1985, 56:876-879.

32. Sethi T, Joshi K, Sharma SC, Gupta BD: Radiation therapy in the management of giant lymph node hyperplasia. Br J Radiol 1990, 63:648-650.

33. Massey GV, Kornstein MJ, Wahl D, Huang XL, McCrady CW, Carchman RA: Angiofollicular Lymph Node Hyperplasia (Castleman’s Disease) in an Adolescent Female: Clinical and Immunologic Findings. Cancer 1991, 68:1365-1372.

34. Veldhuis GJ, van der Leest AHD, de Wolf JTM, de Vries EGE, Vellenga E: A case of localized Castleman's Disease with systemic involvement: treatment and pathogenetic aspects. Ann Hematol 1996, 73:47-50.

35. Beck JT, Hsu S-M, Wijdenes J, Bataille R, Klein B, Vesole D, Hayden K, Jagnannath S, Barlogie B: Brief Report: Allelic expression of interleukin-6 in breast cancer. N Engl J Med 1994, 330:602-605.

36. Weisenberger DD, Nadwani BN, Winberg CD, Rappaport H: Multicentric Angiofollicular Lymph Node Hyperplasia: A Clinicopathologic Study of 16 Cases. Hum Pathol 1985, 16:162-172.