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Quiz Case

Pancreatic head mass: To Whipple or not to Whipple

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The patient was a 57-year-old female with a 3.8 cm, solid, lobulated, and ill-defined pancreatic head lesion suspected to represent a primary pancreatic malignancy. An endoscopic ultrasound (EUS) was performed and EUS-guided fine needle aspiration (FNA) of the pancreatic mass was obtained with rapid on-site evaluation (ROSE). The direct smears showed the following [Figure 1].

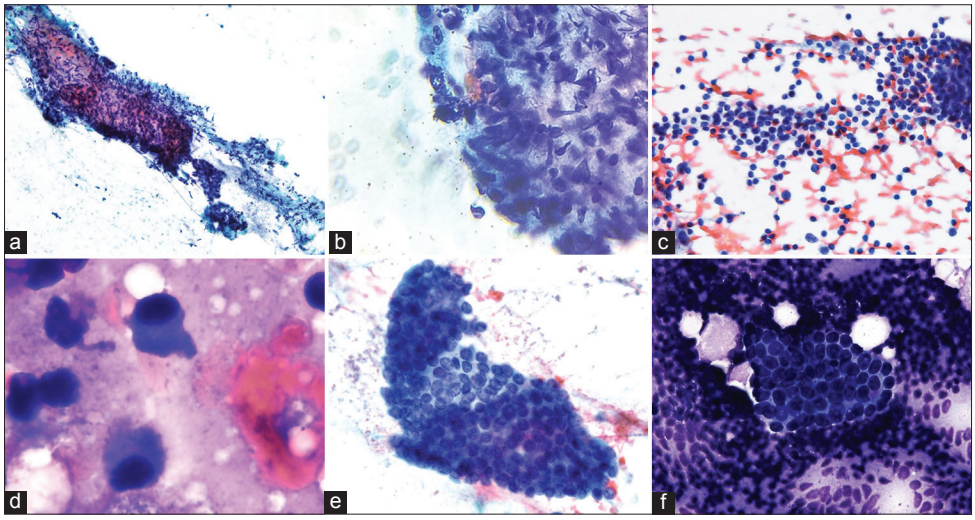

Figure 1: (a) and (b) Fragments of fibrous tissue with dense mononuclear cell infiltrate (Papanicolaou stain, ×20 and ×100, respectively). (c) and (d) Dispersed background lymphomononuclear cells and high-power view of plasma cells. Lymphocytic counts of 27/60X field were identified. Plasma cells were less numerous (8/60X field). (Papanicolaou, ×20 and ×100, respectively). (e) and (f) Ductal epithelium with slight nuclear enlargement and disorganization, consistent with mild atypia (Papanicolaou, ×40 and DiffQuik, ×40, respectively).

QUESTION 1

What is your interpretation?

a. Negative for malignancy; mucinous cyst debris of uncertain etiology
b. Positive (for malignancy); malignant glandular and squamous cells consistent with adenosquamous carcinoma
c. Suspicious (for malignancy); rare markedly atypical epithelial cells suspicious for adenocarcinoma accompanied by fragments of desmoplastic stroma
d. Atypical; cellular stromal elements with mononuclear cells and mild ductal epithelial atypia.

ANSWER TO QUESTION NUMBER 1

The correct cytologic interpretation is: D. Atypical; cellular stromal elements with mononuclear cells and mild ductal epithelial atypia.

The FNA showed numerous fragments of fibrous tissue with a dense lymphomononuclear cell infiltrate present both within the stromal fragments and in the background. Lymphocytic counts of 27/60X field were identified. Plasma cells were less numerous (8/60X field). Immunocytochemical staining for immunoglobulin G4 (IgG4) performed on air-dried smears was non-contributory. Groups of ductal epithelium with mild nuclear atypia were noted. Material was not available for cell block. The case was signed out as, "Atypical; mild ductal epithelial atypia and chronic fibroinflammatory changes."

ADDITIONAL DETAILS, FOLLOW-UP AND BRIEF DISCUSSION

The patient denied alcohol consumption but had a remote history of tobacco use. Prior to detection of the lesion, she had visited the emergency room on two occasions over a 3-month period due to epigastric pain accompanied by weight loss and anorexia. She eventually underwent cephalic duodenopancreatectomy. Macroscopic examination of the specimen revealed an ill-defined, tan, 4 cm lesion within the pancreatic head. Histologic sections of the lesion [Figure 2] showed dense lymphoplasmacytic infiltrates with perineural accentuation, storiform fibrosis, and acinar atrophy. Non-obliterative lymphoplasmacytic phlebitis and non-necrotizing obliterative arteritis were observed. Immunohistochemistry revealed over 50 IgG4-positive plasma cells per high power field and an IgG4 to IgG ratio of over 50%. These findings proved histologically highly suggestive of IgG4-related autoimmune pancreatitis (AIP).

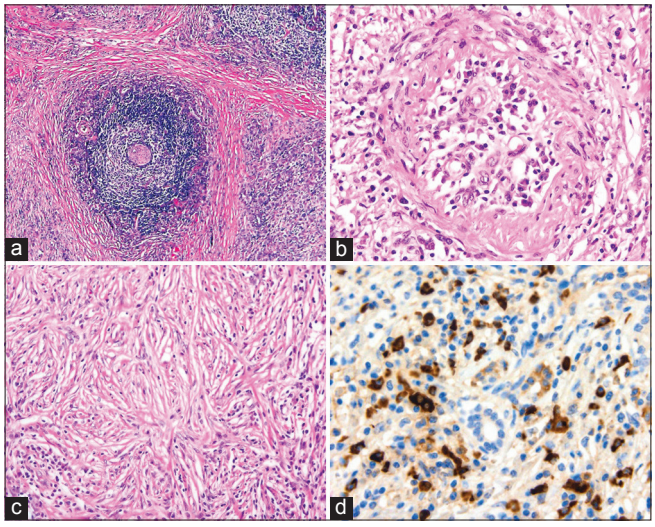

Figure 2: (a) Dense lymphoplasmacytic infiltrate with marked perineural accentuation (H&E, ×4). (b) Obliterative arteritis with recanalization and transmural lymphoplasmacytic inflammatory infiltrate (H&E, ×20). (c) Fibrosis exhibiting a storiform-pattern (H&E, ×20). (d) Numerous immunoglobulin G4 (IgG4)-positive plasma cells (IgG4 immunohistochemistry, ×40).

The patient's serum IgG4 level preoperatively was 85 mg/dL and postoperatively rose to 122 mg/dL. Both values were insufficient to meet the serological diagnostic criterion of 136 mg/dL for IgG4-related disease.[1] However, clinical follow-up was significant for persistent enlargement of abdominal lymph nodes as well as elevated alkaline phosphatase and gamma-glutamyl transferase, presumed to represent IgG4-related lymphadenopathy and cholangiopathy. Prednisone and methotrexate therapy were initiated with subsequent resolution of lymphadenopathy and normalization of liver enzymes. The patient is asymptomatic 2 years after surgery.

It is important to be aware of mass-forming inflammatory lesions of the pancreas such as AIP which may clinically and radiologically simulate pancreatic malignancy sometimes leading to unnecessary surgical resection. Although EUS guided FNA (EUS-FNA) is often a useful adjunct in the diagnosis of pancreatic lesions, allowing for correct classification of many cases, the preoperative diagnosis of AIP based on EUS-FNA is challenging, and no widely accepted cytologic criteria have been reported.[2,3] Furthermore, benign features suggestive of AIP do not rule out false negative results induced by sampling error.[4]

ADDITIONAL QUIZ QUESTIONS

Q2. All of the following are suggestive of Type 1 AIP over Type 2 AIP, EXCEPT:
   a. Systemic disease
   b. Frequent relapses
   c. Swift response to immunosuppression
   d. Inflammatory bowel disease (IBD).

Q3. All are pathological characteristics of Type 1 AIP, EXCEPT:
   a. Lymphoplasmacytic inflammation with storiform fibrosis
   b. Preferential involvement of pancreatic tail
   c. IgG4+/IgG+ plasma cell ratio of >40%
   d. Obliterative phlebitis.

Q4. Which of the following is true regarding the cytomorphologic findings of Type 1 AIP:
   a. Fragments of cellular fibrous stroma are common
   b. Ductal epithelial atypia precludes diagnosis of AIP
   c. Cytologic findings are highly specific and alone are sufficient for a definitive diagnosis
   d. On FNA, AIP is indistinguishable from chronic pancreatitis, NOS.

ANSWERS TO ADDITIONAL QUIZ QUESTIONS AND BRIEF REVIEW OF THE TOPIC

Q2. (d); Q3. (b); Q4. (a).

Q2. (d) AIP is a pancreatobiliary-centric inflammatory disease, typically marked by corticosteroid responsiveness and classified in two groups. Type 1 AIP often affects elderly males, associates extrapancreatic manifestations of systemic IgG4-related disease (including cholangitis, sialadenitis, retroperitoneal fibrosis, or lymphadenopathy), shows frequent relapses and elevation of serum IgG4 in approximately 80% of cases.[5] In contrast, Type 2 AIP is considered to be an isolated pancreatic disorder and does not show elevation of serum IgG4. Recurrence is rare. Interestingly, Type 2 AIP is linked to inflammatory bowel disease (ulcerative colitis or Crohn's disease), seen in up to 16–30% of Type 2 AIP cases.[5,6]

Q3. (b) AIP most often involves the head of the pancreas.[7] Type 1 AIP is histologically characterized by a dense lymphoplasmocytic infiltrate, storiform fibrosis, obliterative phlebitis, and increased numbers of IgG4 positive plasma cells, typically >50/high-power field, and IgG4+/IgG+ ratio of >40%.[8] Lymphoplasmacytic arteritis and a preferentially perineural distribution of inflammation have also been described.[8,9] Type 2 AIP is histologically characterized by periductal inflammation with granulocytic epithelial lesions and relative paucity of IgG4-positive plasma cells.[10]

Q4. (a) EUS-FNA alone is widely considered to be insufficient to make a definitive diagnosis of AIP, probably at least partially due to a lack of architectural integrity.[11] In fact, International Consensus Diagnostic Criteria for AIP (2011) list core/surgical biopsy specimens as preferable for diagnosis of AIP.[12] Despite this, certain cytological findings in conjunction with clinicoradiological clues can aid in establishing a diagnosis AIP in certain cases. A recent retrospective review of AIP FNA results found that cellularity of stromal fragments was significantly higher in AIP than in the control group.[2] Furthermore, stromal fragments with embedded lymphocytes (>30/60x) were seen in almost 40% of AIP cases versus 0% in chronic pancreatitis, NOS.[2] Other authors have found that AIP is often reported as "atypical" on FNA, probably due to ductal epithelial atypia secondary to surrounding inflammatory and fibrotic changes.[4] Performance of IgG4 immunolabeling on the cell block material and/or pre-operative identification of elevated serum IgG4 levels may provide valuable information. Unfortunately, as occurred in the present case, not all cases of Type 1 AIP demonstrate elevated serum IgG4 and cell block material was not available for evaluation.

SUMMARY

Awareness of AIP's potential to clinically and radiologically simulate pancreatic malignancy is important to avoid unnecessary surgery.

Although AIP on FNA lacks specific cytomorphologic features, cellular stromal fragments, mild ductal epithelial atypia and prominent lymphocytic infiltrate are common findings and may support the diagnosis in the proper context.

Corticosteroid responsiveness and elevated serum IgG4 are useful clues which, in conjunction with suggestive cytomorphology, may reduce gratuitous duodenopancreatectomy.

COMPETING INTERESTS STATEMENT BY ALL AUTHORS

The authors declare that they have no competing interests.

AUTHORSHIP STATEMENT BY ALL AUTHORS

AH collected the details of the case, carried out literature review, and drafted the manuscript. APC conceptualized the case, and edited the manuscript. ERS and CI performed data review and review of the manuscript.

ETHICS STATEMENT BY ALL AUTHORS

Given that this case is without identifiers, our institution does not require approval from the Institutional Review Board.

LIST OF ABBREVIATIONS (In alphabetic order)

AIP – Autoimmune pancreatitis
EUS – Endoscopic ultrasound
FNA – Fine needle aspiration
GGT – Gamma-glutamyl transferase
IBD – Inflammatory bowel disease
IgG4 – Immunoglobulin G4
MRI – Magnetic resonance image
NOS – Not otherwise specified
PET-CT – Positron emission tomography - computed tomography
ROSE – Rapid on-site evaluation

EDITORIAL/PEERREVIEW STATEMENT

To ensure the integrity and highest quality of CytoJournal publications, the review process of this manuscript was conducted under a **double-blind model** (the authors are blinded for reviewers and vice versa) through automatic online system.

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