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High-grade appendiceal mucinous neoplasm: Report a case

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ABSTRACT

Appendiceal mucinous neoplasm (AMN) includes a group of diseases which are classified into Low grade and high grade appendiceal mucinous neoplasm (LAMN and HAMN) respectively. These rare tumors have limited published data and more trials are required to grasp a better understanding of the disease. In this report, we discuss a rare case of HAMN in a 54-year-old Nepalese male presenting to our hospital complaining of right lower abdominal pain for 7 days associated with Nausea, vomiting and anorexia. On examination abdomen was soft, mildly distended with severe right iliac fossa tenderness and positive rebound tenderness. A presumptive diagnosis of complicated appendicitis was made. However, the final diagnosis of HAMN was made after the pathological specimen was resected surgically by laparoscopic appendectomy and was sent for histopathology. Our case report highlights the importance of including HAMN as a differential for complicated appendicitis cases especially in patients at their 60 decades.

Keywords: Appendiceal mucinous neoplasm, Pseudomyxoma peritonei, High grade, Diagnosis

1. INTRODUCTION

AMN is defined as appendiceal epithelial neoplasms characterized by mucinous epithelial proliferation with extracellular mucin with pushing tumor margins (Misdraji et al., 2019). If the appendix perforates and the mucin deposits into the peritoneum it can lead to a lethal called pseudomyxoma peritonei (PMP). AMN encompasses a heterogeneous group of diseases which are classified into LAMN and HAMN. Usually what differentiates these subtypes is the degree of atypia found microscopically. These tumors are considered to be very rare, they constitute around < 1% of all types of cancers (Shaib et al., 2017). HAMN is a relatively recently introduced term and it remains understudied (Carr et al., 2016). In 2019, the World Health Organization has distinguished appendiceal mucinous neoplasms from appendiceal adenocarcinoma as a different entity (Shaib et al., 2017). As a result of its rare incidence and recent recognition, HAMNs has very limited data and publications and the discussion regarding their pathology and clinical characteristics are insufficient. In our report, we are introducing a case

of a 54-year-old Nepalese male who presented as complicated acute appendicitis which eventually was diagnosed histologically as HAMN.

2. CASE REPORT

A 54-year-old Nepalese male not known case of any medical disease presented to Accident and Emergency Department at Salmaniya Medical Complex on 17/6/2022 with Complaint of Right lower abdominal pain of 7 days duration associated with Nausea, vomiting and anorexia. No History of fever or any other complaints. On examination patient was vitally stable, abdomen was soft, mildly distended, and right iliac fossa severe tenderness was noted with positive rebound tenderness. Laboratory findings showed high white blood cells count mainly neutrophils with elevated C- reactive protein. Abdominal Ultrasound, Chest and Abdominal X Rays were performed, as well as Computed Tomography (CT) scan of Abdomen and pelvis. Abdominal ultrasound findings were suggestive of complicated appendicitis. Chest X ray was normal with no air under the diaphragm to exclude any perforations.

Computed Tomography Scan (CT) scan showed a large dilated enhancing wall appendix measuring about 4 cm in maximum dilation, containing multiple air pockets seen at medial aspect cecum. Significant surrounding fat stranding and inflammatory changes seen around the appendicular lesion (Fig. 1). No free gas. Reactionary thickening of the cecum and terminal ileum is noted, otherwise no small or large bowel abnormal thickening or dilatation. Liver, gallbladder, pancreas, spleen, both kidney and both adrenal glands show no significant lesion. Small right sided renal cyst is noted measuring 0.7 cm. No significant enlarged lymph nodes by size criteria, Normal abdominal vascular structures. Urinary bladder and prostate are unremarkable. No significant bony lesions could be seen. Basal lung cuts unremarkable. Upon these results, patient was admitted as complicated acute appendicitis and the decision of laparoscopic appendectomy under general anesthesia was done.

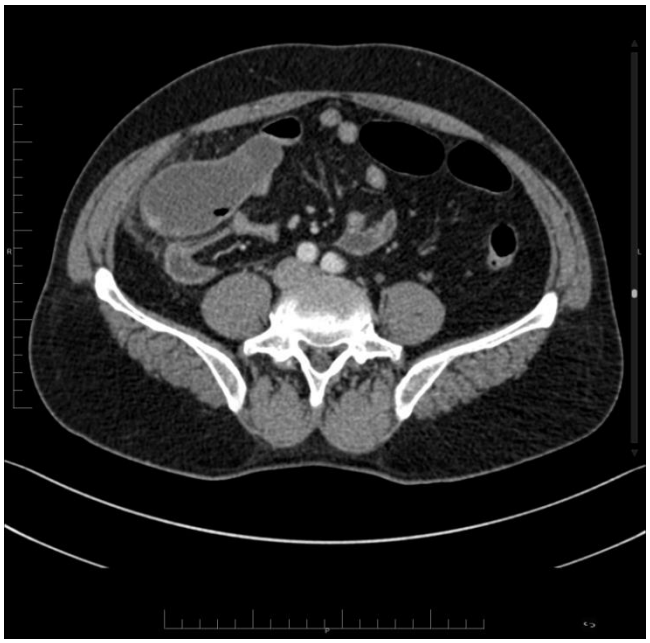
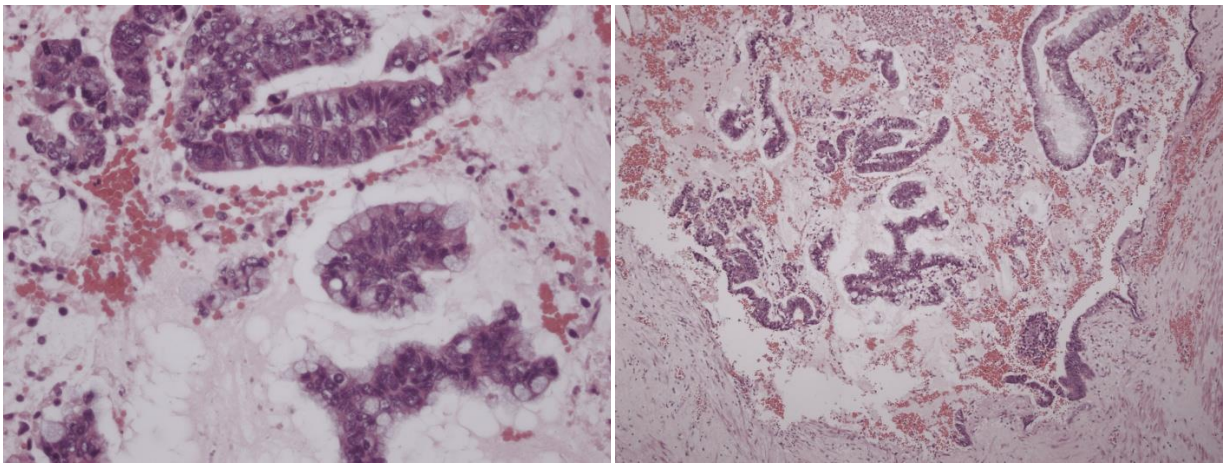


Figure 1 Computed tomography scan of Abdomen and pelvis (CT scan) Showing large dilated enhancing wall appendix measuring about 4 cm in maximum dilation, containing multiple air pockets seen at medial aspect cecum. Significant surrounding fat stranding and inflammatory changes seen around the appendicular lesion

The surgical findings during the operation were as follow; Enlarged appendix that is acutely inflamed, gangrenous, perforated at mid-section with minimal pus formation, wide base, healthy cecum and reactionary free fluid. The appendix specimen was sent to histopathology for further investigation. On gross examination specimen was labeled as appendix, received fixed in formalin. It consists of an appendix with attached fat measuring 10.5 cm in length and 4.5 cm in diameter. The outer surface was congested and intact. Cut surface shows mucinous material. Microscopic examination on the other hand showed high-grade features, enlarged pleomorphic nuclei with hyperchromasia and abundant atypical nuclear mitosis. Clear pools of mucin were seen as well (Fig. 2). Tumor and acellular mucin invade through muscularis propria into subserosa but does not extend to serosal surface. No Lymphovascular or perineural Invasion was noted. Two reactive lymph nodes were seen. The histologic Grade was G1, well

differentiated. These findings are all coherent with the final diagnosis of High grade appendiceal mucinous neoplasm (HAMN), pT3NOMX, margins free.

Post operatively was uneventful. Patient was doing well, no complications. He was admitted in the hospital for 4 days, was on analgesia and antibiotics. He started feeding orally post operatively and he tolerated it well. Patient was discharge on 21/6/2022 and was scheduled for follow up appointment at surgical clinic after 2 weeks. According to the surgical plan next step should be staging CT of chest and possible right hemicolectomy.



A **B**

Figure 2 (A: Low power view X10, B: High power view X40) – Hematoxylin and eosin stain (H&E) High-grade features, markedly enlarged pleomorphic and hyperchromatic nuclei with abundant atypical nuclear mitosis. Clear pools of mucin are seen as well.

3. DISCUSSION

Appendiceal mucinous neoplasms are mucinous tumors in which the epithelium is dissecting into the muscularis mucosae, however they must be limited to muscularis propria and should not be infiltrative or have a stromal desmoplastic reaction (Carr et al., 2016). This umbrella term comprises a diverse group of diseases which are classified into LAMN and HAMN only if there are high-grade dysplastic changes (Carr et al., 2016). If the appendix ruptures in this case the term psudomyxoma peritonei is used. PMP is defined as a clinical term in which there is the appendiceal mucinous neoplasm accompanied with spread of abundant mucin in the peritoneal cavity. The outcome and ultimate prognosis in such cases depends mainly on the availability of neoplastic cells within the extra-appendiceal mucin or not (Carr et al., 2017).

These tumors are considered to be relatively rare. Annually in America, it is reported around 3500 cases only (Choudry and Pai, 2018). There is no gender preference in the distribution of these tumors. The age of incidence is usually in the 60s; however there can be a wide age range (Misdraji et al., 2019). In 2013 there was a study done on 17 cases of interval appendectomies for complicated appendicitis, it revealed that 5 out of 17 patients were eventually diagnosed with appendiceal mucinous neoplasm (Furman et al., 2013). This proves that incidence of these tumors is more commonly seen in complicated appendicitis cases rather than simple acute appendicitis.

Clinically, those Patients present with the complaint of appendicitis- like symptoms. Moreover, if there is appendicular rupture they will be having diffuse abdominal distention due to the fatal condition PMP. Nevertheless, appendiceal mucinous neoplasms usually are incidentally diagnosed either during imaging, endoscopy or histopathology results (Hamilton and Stormont, 1989, Mizuma et al., 1997). As it was seen in our case in which there was classical picture of complicated appendicitis until the pathology report revealed the typical histological findings of HAMN.

Radiological findings are nonspecific. However, increase in appendiceal diameter estimated more than 15 mm (Tirumani et al., 2013), presence of wall thickening or soft tissue mass can all be suggestive findings seen in mucinous neoplasm. These tumors depend primarily on the histologic subtypes to determine their disease course and prognosis (Carr et al., 1995). Hence lays the importance of the histopathological examination of the appendix specimen. Grossly, in both LAMN and HAMN, if the appendix is intact, it will most likely be enlarged as a consequence of mucin accumulation within it. In cases where there is appendicieal perforation mucin extrusion may be evident. In our case, the gross examination demonstrates an appendix measuring 10.5 cm in length and 4.5 cm in diameter. The outer surface was congested and intact and cut surface showed mucinous material. Microscopic

examination reveals slight difference between LAMN and HAMN and it might be the sole source to differentiate between these very similar tumors subtypes.

In LAMN, villous proliferation of mucinous epithelium with mucin vacuoles seen in cytoplasm and compressed bland nuclei or epithelial scalloping with columnar cells with nuclear pseudostratification, a broad pushing margin, various degrees of extracellular mucin, with atrophy of lymphoid tissue, loss of crypts and calcification fibrosis and hyalinization of the appendiceal wall (Misdraji et al., 2019). Meanwhile in HAMN, findings are approximately similar to those of LAMN. However, you might encounter convoluted architecture presenting as micropapillary features, cribriform growth, piling up of epithelial cells with high-grade features such as enlarged, hyperchromatic, and pleomorphic nuclei with multiple atypical mitotic figures, single-cell necrosis and sloughed necrotic epithelial cells in the lumen (Misdraji et al., 2019). In case of perforation, Extra-appendiceal mucin, epithelium or both may be seen which are very important to document due to its outcome on overall disease prognosis (Misdraji et al., 2019). It is worth noting that the infiltrative invasion which is seen in mucinous adenocarcinoma is not seen in both LAMN and HAMN. In spite of the fact that HAMNs seem to be more drastic compared to LAMNs, the treatment regimen and management is similar to LAMNs rather that of mucinous adenocarcinomas (Carr et al., 2016).

A recent study that was done on 35 cases of HAMN showed that grossly the mean tumor size was 7.9 cm. Gross perforations with mucin was seen in 14 cases. Microscopically, the distribution of high-grade atypia was diffuse in which it was involving the entire appendix in 20 cases, but non diffuse in 15 cases. Atypical architecture pattern was seen, such as micropapillary, cribriform, multilayered epithelial growth. However, 16 out of 35 cases were showing none of these changes. In case of PMP the most common sites involved at presentation where omentum, peritoneum, bowel serosa, and the ovaries in females (Gonzalez et al., 2022). As for the staging of these tumors, if Both LAMN and HAMN are confined to the appendiceal wall without invasion or loss of the muscularis propria they are staged as pTis. If the tumor perforates into subserosa it is pT3. If the tumor involves the serosa it is considered as pT4a. HAMNs are staged similarly as invasive adenocarcinoma. Mucin involving distant peritoneal sites is classified as M1. In case of acellular peritoneal deposits, it is staged pM1a, and if the mucin was cellular and contains mucinous epithelial cells its pM1b (Misdraji et al., 2019).

The prognosis of such tumors depends principally on whether the tumor is limited to the appendix or is extra-appendiceal. Clearly in case the mucinous lesion is limited to the appendix it will have a better prognosis as opposed to the lesions with extra-appendieal spread. Extra-appendiceal acelluar mucin has lower risk of recurrence and progression while extra-appendiceal mucin with cellular epithelium has higher risk (Yantiss et al., 2009; Pai et al., 2009). In view of the relatively new recognition of LAMNs and HAMNs, there are limited data proving conventional management guidelines for treating these tumors and more trials are required to outline these standardized treatment procedures. Currently most researchers undertake that for lesions limited to the appendix, simple appendectomy is the treatment of choice (Yantiss et al., 2009). Furthermore, right hemicolectomy is considered for tumors measuring more than of equals to 2 cm, positive margins, or when high-grade histological features seen (Lu et al., 2021). For disseminated peritoneal disease, patients should be sent to specialized centers for more advance management such as hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (Glehen et al., 2010).

4. CONCLUSION

In conclusion, patients with HAMN may have vague presentation and can easily be mistaken as a complicated appendicitis. Thus, Physicians must include HAMNs and other mucinous neoplasms in their differential diagnosis of appendicitis similar cases because these lesions must be recognized pre-operatively and handled with extra precautions during operation due to the risk of rupture and subsequent PMP. HAMNs are rare entities and relatively newly introduced diagnosis and combined efforts must be made from pathologists and surgeons in order to gather more information and have a clearer understanding of it.

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Author's contributions

Equal contribution of all authors.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. No Patient identifying information was included in this manuscript.

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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