Pulmonary pleura metastasis from low-grade appendiceal mucinous neoplasm with appendiceal neuroendocrine tumor: A Case Report

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Research Article

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Abstract

According to the recent World Health Organization (WHO) classification, appendiceal mucinous tumours include low-grade mucinous appendiceal neoplasm (LAMN), high-grade mucinous appendiceal neoplasm (HAMN), and mucinous adenocarcinoma. LAMN is almost the rarest appendiceal tumor with an incidence of about 0.7–1.7%. A ruptured appendiceal mucinous neoplasm can lead to progressive accumulation of mucus in the peritoneal cavity, resulting in pseudomyxoma peritoneum (PMP) with the chance of metastasis and recurrence. Appendiceal neuroendocrine tumor (ANET) is the most frequent appendiceal lesion. A collision between LAMN and ANET is an exceedingly rare condition. So far, evaluating the literature, just 10 cases of collision LAMN and ANET have been reported. Here, we report a case of pulmonary pleura metastasis from LAMN with ANET. Our work will help to improve the accuracy of the diagnosis and avoid misdiagnosis.

1. Introduction

Epithelial neoplasia of the appendix is grouped into LAMN, HAMN, serrated polyp, adenoma, and adenocarcinoma [1]. LAMN accounts for 73% of mucinous epithelial neoplasms. Ladies are more often affected and the pinnacle occurrence is in the 6th decade of life. LAMN is described by the supplanting of normal appendiceal mucosa with an undulating, or flat mucinous epithelial [2]. “Pushing invasion” through the appendiceal wall represents a typical pattern for LAMN [3]. LAMN has a benign morphologic appearance and aggressive biological potential. When LAMN reaches out through the muscularis propria regularly, it results in numerous mucus on the peritoneal membrane, named pseudomyxoma peritoneum (PMP). The possibility to develop a malignant condition is increased when patients have a positive margin; or appendiceal rupture [4, 5]. However, extraperitoneal metastasis of LAMN is extremely rare. LAMN have malignant biological behaviors that are inconsistent with their low-grade cytological characteristics. Currently, fewer than 10 cases of lung metastasis from LAMN have been reported. The earliest report described pulmonary metastases in a patient with an appendiceal mucocele by Berge. Mortman et al. reported 3 similar cases, and Lauren Xu et al. reported 1 similar case [6].

ANET involves around 30–80% of all appendiceal tumors. The vast majority of ANET have an excellent prognosis, with a 5-year survival rate near 100% in the early tumor stages [3]. A collision between LAMN and ANET is an exceedingly rare condition. They are the consequence of two particular neoplasms, without any transition zone, resulting from the proliferation of two different cellular lines. Reviewing and investigating the literature, only 10 other cases of collision LAMN and ANET are reported worldwide [7, 8, 9]. The preoperative diagnosis of LAMN is challenging, especially when LAMN and PMP exist simultaneously.

In our case, we described the histopathological aspects of an unusual pulmonary pleura metastasis from LAMN with ANET. Accurate and standardized pathological diagnosis of this disease is very important for the selection of the treatment.

2. Case Report

A 48-year-old Chinese woman was found to have an elevated CEA during a physical examination. PET-CT showed there were tumorous lesions in the right pleura, appendix, and pelvic. Open exploratory surgery revealed an enlarged appendix. There was scattered mucus on both the omentum and the right suprahepatic diaphragm. Right hemicolectomy, total hysterectomy, and double adnexectomy were performed. During the surgery, a little mucus was seen in the pelvic cavity, the bladder, under the diaphragm, the serous surface of the right uterine horn, the hysterorectal fossa, and the peritoneum on both sides of the uterus. The appendix was 3.5 cm long and 0.4–0.5 cm in diameter. There was a tumour on the serosal surface with a size of 3.4 cm × 2.2 cm × 2.0 cm. The section was gray-white, and some parts were jelly-like. Bilateral ovaries, fallopian tubes, myometrium, and mucosa of the uterine body were not involved by the lesions.

Histopathologic evaluation in LAMN showed the normal mucosa of the appendix was replaced with an undulating epithelial monolayer of uniform columnar cells. LAMN tumour cells were close to the sclerotic fibrous stroma rather than lamina propria with low-grade atypia (Fig. 1-A). Lymph node metastasis: 0/27. The surgical resection margins in both ends of the intestine were negative for malignant cells. In ANET, large and small nests were composed of polygonal cells with salt-and-pepper chromatin and basally-located granules. No mitosis was observed (Fig. 1-B). ANET invaded the serosa of the appendix, with nerve invasion and no vascular invasion. There was an undulating epithelial monolayer of uniform columnar cells with apical mucin in the pulmonary pleura. The morphology of tumour cells was consistent with LAMN (Fig. 1-C). Immunohistochemistry and special staining were done in the LAMN and lung pleura. The results were positive for CK (pan) and D-AB/PAS staining. The ANET cells were positive for CgA, Ki67(1%+), SATB2, SSTR, Syn, CD56 by immunohistochemistry. Elastic fiber staining showed that the pulmonary pleura was intact, indicating that LAMN was transferred to the pulmonary pleura via the esophageal lacuna. (Fig. 1-D).

The Immunohistochemistry and special staining results showed that this tumour in our case was pulmonary pleura metastasis from LAMN with ANET. The treatment and prognosis of this advanced tumour are also different from LAMN and ANET. Therefore, an accurate and standardized pathological diagnosis of this collision tumour is very important for the treatment. In conclusion, a clinical diagnosis of pulmonary pleura metastasis from LAMN with ANET was confirmed by expert consultation.

3. Discussion

LAMN is extremely rare, with no specific clinical manifestations. Histologically, LAMN has low-grade cytological characteristics. However, it is easy to develop into PMP with recurrence and metastasis, so regular follow-up is required. Attention should be paid to observing the position of the tumour and the distance between the tumour and the margin. The pathologist needs to examine the serosal surface of visible mucus and solid areas. It is difficult to distinguish appendiceal mucinous tumours from ovarian

mucinous tumours because of the close location and the nonspecific serum tumour markers, increasing the challenge of diagnosing LAMN [10].

Early and accurate diagnosis has a great significance for the prognosis of patients. Therefore, pathologists especially need to make a distinction between LAMN and the following types of similar tumours. Histologically, prominent features of LAMN are atrophy of submucosa and lamina propria at the lesion, but the mucosal muscular of serrated polyps/adenomas is intact. Furthermore, LAMN produces much mucus, but serrated polyps/adenomas have not [11]. HAMN has papillary and sieve structure, and the tumour cells showed considerable atypia, polymorphonuclear and pathological mitosis. LAMN often has low-grade cell atypia [11]. A villous adenoma is similar to LAMN and can be arranged in villous shape, but LAMN tumour cells are close to the sclerotic fibrous stroma rather than lamina propria. Mucinous adenocarcinoma often grows infiltratively, with single cells, small cell clusters, or irregular glands, often accompanied by the interstitial reaction. Mucinous adenocarcinoma cell atypia and pleomorphism are obvious. In immunohistochemistry, LAMN usually expresses CK (pan), CDX2, and SATB2, which suggested the origin of the lower gastrointestinal tract [13]. Without PAX8 expression, LAMN can be distinguished from ovarian mucinous tumours. The microsatellite is stable in LAMN [12]. There are usually KRAS / GNAS co-mutations in LAMN and ovarian mucinous tumors are usually accompanied by KRAS and CDKN2A mutations [13]. The presence of a collision between LAMN and ANET is exceedingly rare. In ANET, large and small nests were composed of polygonal cells with salt-and-pepper chromatin and cytoplasmic brightly eosinophilic basally-located granules. ANET cells were positive for SSTR2, CgA, and Syn. In this case, the lesion at the pulmonary pleura was confirmed as a LAMN metastasis via immunohistochemical staining and morphology. The elastic fiber staining showed that the pleura was intact, confirming that LAMN metastasized to the pulmonary pleura via the esophageal fissure.

There is no consensus regarding surgical treatment for LAMN. For patients without extra-appendiceal disease, appendectomy and follow-up are recommended. Right colectomy should not be performed, since it gives no advantage for patients with LAMN [14]. Some experts suggest a simple cecectomy in the case of a mucinous neoplasm with positive margins and negative appendiceal lymph nodes. Peritoneal mucus should be cleared and hyperthermic intraperitoneal perfusion chemotherapy (HIPEC) should be performed on LAMN patients with PMP [14]. In this case, the patient underwent right hemicolectomy, omentum resection, cauterization of peritoneal lesions (sub-diaphragm, rectal fossa of the uterus, retroflexed peritoneum of the bladder, parametrium), total hysterectomy, bilateral adnexal resection, and HIPEC. Currently, follow-up is recommended to start yearly, including an abdominal computed tomography (CT) scan and determination of serum tumour markers. Furthermore, CA125, CA19-9, and CEA are significant prognostic elements to predict patients' prognosis [15]. Our case is rare, and its description and report will help in the diagnosis of the pulmonary pleura metastasis from LAMN with ANET.

4. Conclusion

In summary, an extremely rare case of pulmonary pleura metastasis from LAMN with ANET has been reported that combined morphology, immunohistochemistry, and special staining. Early and precise pathological reports and adequate surgery are the keys for either cure or achievement of longer overall survival.

Declarations

Ethics Statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author Contributions

The first author (J, G) wrote and edited the final manuscript. The second author (RR, F) performed the lab work. The corresponding author (MZ, L) guides the manuscript writing.

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Conflicts of interest

The authors declare that they have no conflict of interest in this case report.

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Figures

Figure 1

H&E, Immunohistochemistry, and special dyeing. **(A)** H&E in LAMN. The normal mucosa was replaced with an undulating epithelial monolayer of uniform columnar cells with apical mucin **(red arrow)**. **(B)** H&E

in ANET. Large and small nests were composed of polygonal cells with salt-and-pepper chromatin and eosinophilic granules. In immunohistochemistry analysis **(middle)**, the ANET cells were positive for SYN and the Ki-67 was about 1%. **(C)** H&E in the pulmonary pleura: There was an undulating epithelial monolayer of uniform columnar cells with apical mucin in the pulmonary pleura. The morphology of tumour cells was consistent with LAMN **(red arrow)**. The black arrow showed that the pulmonary pleura is intact. **(D)** Elastic fiber staining showed that the pulmonary pleura was intact **(black arrow)**, indicating that LAMN was transferred to the pulmonary pleura via the esophageal lacuna.