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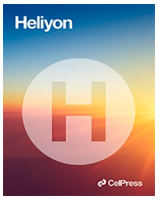

Case report

Primary mucinous adenocarcinoma of the anterior mediastinum with *HER-2* mutation: A rare case report

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ABSTRACT

We report the case of a 68-year-old male whose Computed Tomography (CT) scan presented a mass (68*62*54 mm) of the right anterior mediastinal and pathologically diagnosis was mucinous adenocarcinoma(MA). The peripheral vessels are surrounded by the big mass in the anterior mediastinum which was associated with multiple metastases, thus we performed palliative chemoradiotherapy and we tried Human Epidermal Growth Factor Receptor-2 (HER-2) inhibitors based on the Next Generation Sequencing. The patient passed away 16 months after the onset of the disease. In this report, we review the rare case of anterior mediastinum MA as well as perspectives for potential future treatments.

1. Introduction

Mucinous adenocarcinomas(MAs) are relatively common types of adenocarcinomas with specific immunohistochemical profiles [1]. The typical locations of MAs include gastrointestinal tract, breast and ovary,it is extremely rare for MAs to originate from the mediastinum [2]. To date, only 19 cases of anterior mediastinal MAs have been reported (Table 1). Adenocarcinomas of the mediastinum can be subtyped as papillary and nonpapillary adenocarcinomas [3]. Among these, MA is a relatively uncommon pathological subtype of nonpapillary adenocarcinomas [4].

In this report, we present a case of primary anterior mediastinum MA with HER-2 mutation.

2. Case presentation

The patients of our case was a 68-year-old man with abnormal chest CT scan revealed an anterior superior mediastinal mass causing peripheral vascular compression and deviation (Fig. 1). The clinical stage of the patient was stage IV due to metastasis in the 8th rib, thoracic vertebra, lumbar vertebra (Fig. 3a) and ilium. He was a heavy smoker (smoking index = 2000) and his parents were all diagnosed with cancer. He had hypertension and coronary heart disease for 3 years. A needle biopsy of the mediastinal mass revealed MA with neuroendocrine differentiation, with cells arranged in cuplike or nest patterns and abundant mucus (Fig. 2). Pathological Results: (anterior mediastinum) mucinous adenocarcinoma. Immunohistochemical results: CK7(−), CK20(+), CK5/6(−), Villin(+), CD56(−), CgA(−), Syn(−), TTF-1(−), SATB2(−), MUC5ac(−), MUC2(+), NaspinA(−), p63(−), Calponin(−), S-100(−), MSH6(+),

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Table 1
Summary of previously reported cases of anterior mediastinum MA.

Reference	Sex Age	Tumor size (mm)	IHC results		Treatment	Outcome
			Positive	Negative		
Current case	M/67	68 × 62 × 54	CK20; TTF-1; CDX2; MUC2; CD56	CK7; SATB2; MUC5ac;	Surgery; Radiotherapy; Chemotherapy	Dead (16 months)
Tsukaguchi et al. [5]	F/39	70 × 40	CK20; CDX2	CK7; CD5; TTF-1; synaptophysin	Chemotherapy; Lenvatinib	Dead (5 months)
Hamahiro et al. 6	M/68	60	CK20; CDX2	CK7; CD5; TTF-1; estrogen receptor	Chemotherapy	Dead (6 months)
Tomoshige et al. [6]	M/74	60	CD5; CK7; PAX8	TTF-1; CDX2; CK20	Surgery	Dead (6 months)
Koo et al. [7]	F/60	69 × 64 × 49	CDX2; CK7; CK20; MUC2	TTF-1	Surgery; Radiotherapy; Chemotherapy	Alive (15 months)
Himuro et al. [8]	M/58	75	CDX2; CEA; CK7; CK20	CD5; CD117; TTF-1	Surgery; Radiotherapy	Dead (6 months)
Kinoshita et al. [9]	F/79	94 × 76 × 51	CDX2; CK20	CK7	Surgery	Alive (15 months)
Maeda et al. [10] (Case 1)	F/52	95 × 60 × 55	CK20; CDX2; CEA; CD5	CK7; TTF-1	Surgery; Radiotherapy; Chemotherapy	Alive (11 months)
Maeda et al. [10] (Case 2)	M/38	80 × 70 × 35	CK20; CDX2; CEA; CD5; CK7	TTF-1	Surgery; Radiotherapy; Chemotherapy	Dead (12 months)
Maeda et al. [10] (Case 3)	M/55	130 × 70 × 45	CK20; CDX2; CEA; CD5	CK7; TTF-1	Surgery; Radiotherapy; Chemotherapy	Dead (24 months)

Abbreviations: F,female; M,male.

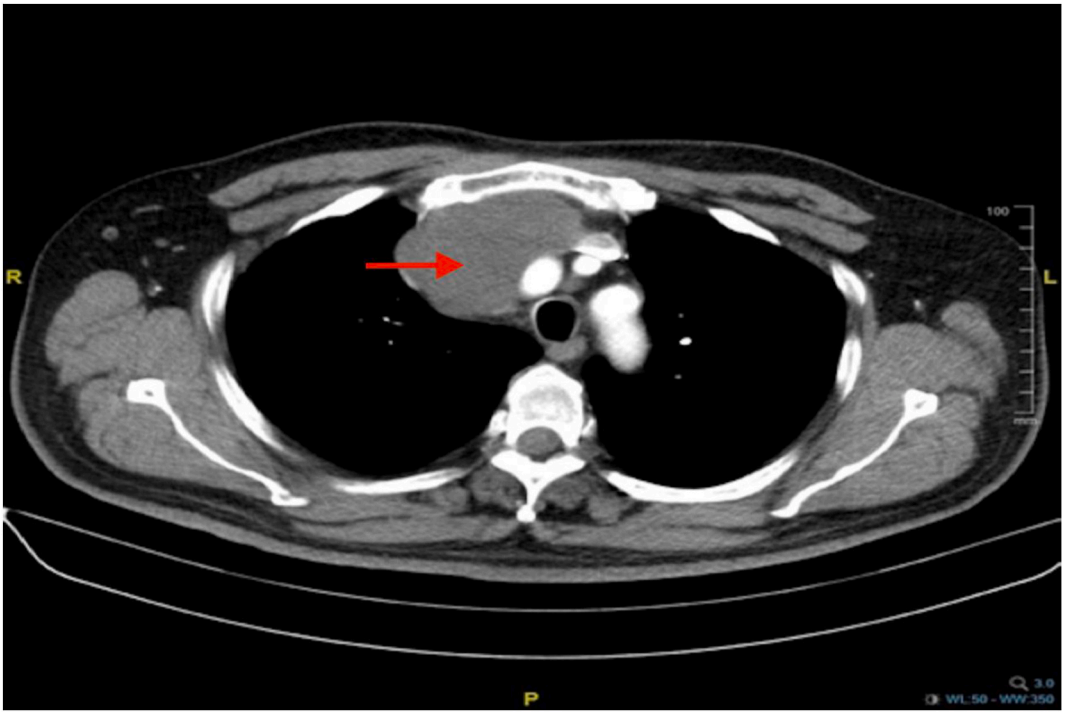

Fig. 1. Chest CT scan image demonstrating the soft tissue mass of the anterior superior mediastinum (measuring 68 × 62 × 54 mm).

MSH2(+), MLH1(+), PMS2(+), Ki-67(70 %). The tissue was subjected to next-generation sequencing, yielding the following results: PD-L1 (TPS <1 %, CPS <1), TMB = 5.76 Mutations per Megabase (Muts/Mb), and it was Microsatellite Stable (MSS). Importantly, the primary tumor was positive for HER2 mutation (p.R678Q with a mutation frequency of 37 %), CCND2 amplification and CDK4 amplification.

The patient experienced worsening back pain and paralysis of both lower limbs after hospitalisation due to vertebral bone fracture (Fig. 3a). There are no standard treatments for mediastinal MAs, in order to relieve the patient's symptoms as quickly as possible, the patient decided to underwent posterior thoracic vertebral tumor resection, spinal decompression, and pedicle screw internal fixation after consulting the surgeons. The patient recovered well postoperatively and underwent palliative mediastinal mass radiotherapy

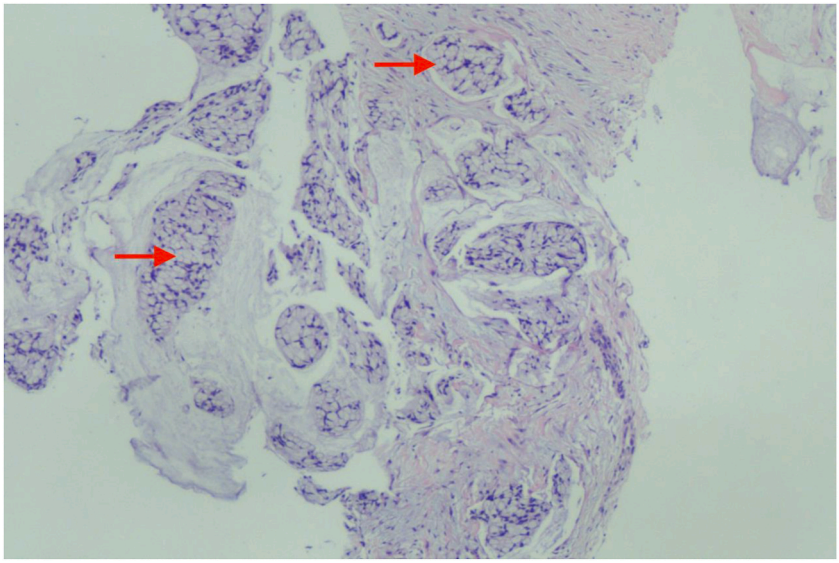

Fig. 2. Photomicrograph of the patient that mucinous cells arranged in cuplike or nest patterns.

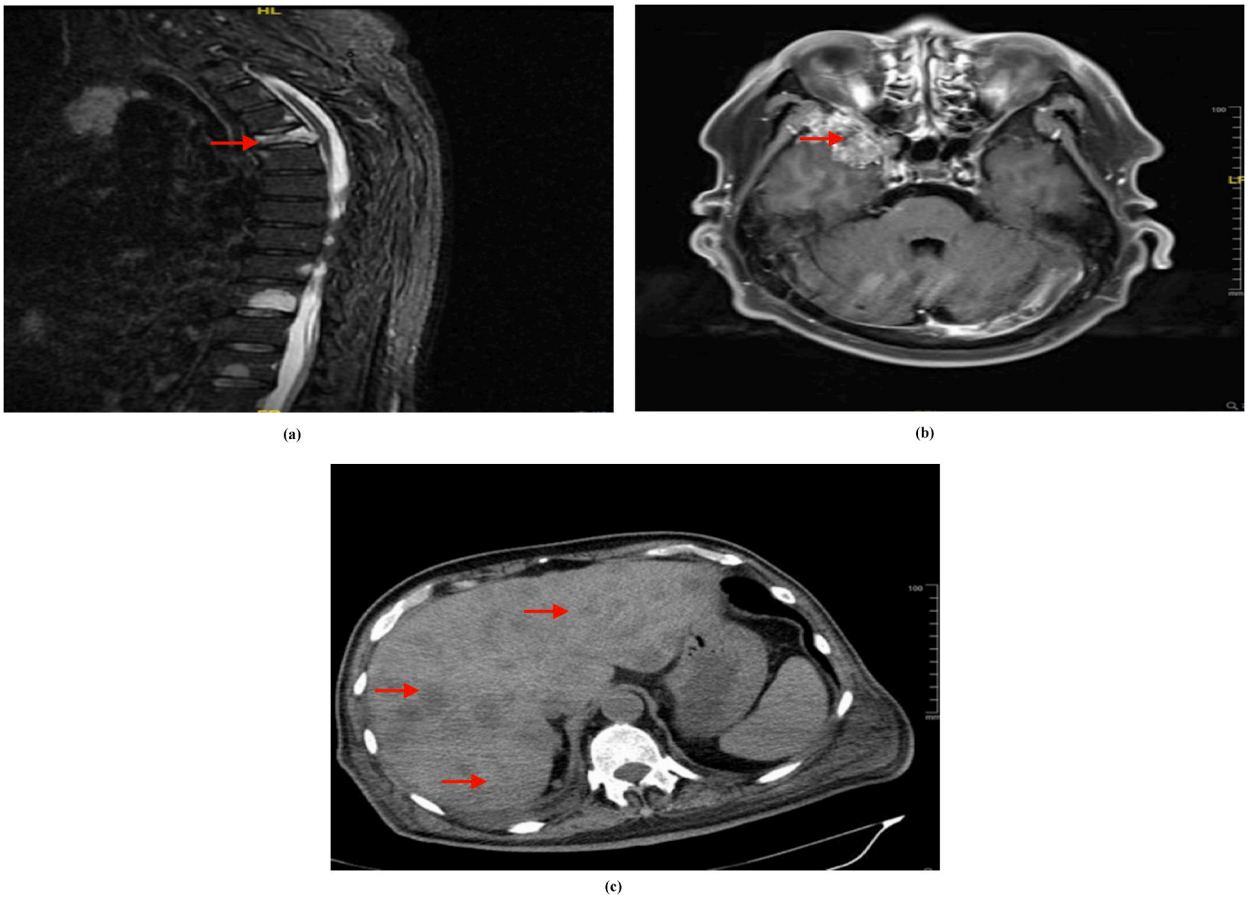

Fig. 3. (a)Magnetic Resonance Imaging of metastases and bone fracture of the vertebra; (b) Single metastasis of the right temporal lobe; (c) CT scan of diffuse liver metastases.

with a dose of 50Gy to control the primary lesion. After irradiation, a CT scan revealed a new mass in the right lower lobe of the lung which was also biopsied. The patient then received four cycles of chemotherapy (pemetrexed + cisplatin + bevacizumab) and radiotherapy for the thoracolumbar segmental and lung metastases to further reduce the tumour burden. 8 months after diagnosis, magnetic resonance revealed brain metastasis (Fig. 3b)and the patient underwent local radiotherapy for the brain. 14 months after diagnosis,PET-CT scan showed disease progression in the liver (Fig. 3c), lung, bone marrow, and supraclavicular lymph nodes. Genetic testing of the supraclavicular metastatic lymph nodes revealing the continued presence of the HER2 p.R678Q mutation but at a higher frequency of 83.2 %. Since tumors with HER2 mutations may be sensitive to HER2 inhibitors, we recommended Trastuzumab + Pyrotinib treatment based on the next-generation sequencing results. However, the patient stopped taking the medication after two months due to the deterioration of his condition and sadly passed away 16 months after the onset of the disease.

3. Discussion

MA is a distinct subtype of adenocarcinoma characterized by the presence of abundant intracellular and extracellular mucin, which accounts for at least 50 % of the tumor volume [11]. In this paper, we present a case of primary anterior mediastinal MA with HER2 mutation. Understanding this subtype can be crucial in preventing misdiagnosis as metastatic disease originating from an extrathymic primary source.

While it is crucial for diagnosis and treatment, determining the primary lesion remains a significant challenge. In this study, we have reviewed previous cases, including the results of immunohistochemistry, treatment modalities, and prognosis [5–10,12] (Table 1). Immunohistochemical analysis of the cases reported previously exhibited similar characteristics to our case. Specifically, our case exhibited positive expression of CK20 and CDX2 but negative expression of CK7(Fig. 2). Therefore, the positive expression of CK20 and CDX2 raised suspicion of gastrointestinal carcinoma metastasis [13]. Thus we conducted gastroenteroscopy and PET/CT, both of which did not reveal any signs of alternative malignancies. Additionally, needle aspiration findings of lung metastasis excluded the possibility of enteric-type adenocarcinomas of the lung. Enteric-type adenocarcinoma of the thymus is a rare type of adenocarcinoma that originates from the mediastinum but morphologically and immunohistochemically similar to colorectal cancer. Although it can also express CDX-2 and CK20, MAs produce large amounts of mucins and glycoproteins around the tumor and are less likely to form glandular structures which can be used to differentiate them.Consequently, our multidisciplinary treatment team concluded that the mediastinal mass was indeed a primary MA with features of enteric differentiation.

Because of the lack of standard therapy for mediastinal MAs, patients may benifit from personalized treatment based on the mutation profile. A 39-year-old woman was diagnosed as thymic mucinous carcinoma with PIK3CA mutation and underwent paclitaxel–carboplatin-based chemotherapy and lenvatinib. Despite treatment, it failed to suppress the tumor. The association between PIK3CA and resistance to lenvatinib was suspected [5]. In this study, we assess the feasibility of an innovative approach based on molecular testing. Reviewing genetic test results from previous studies on MAs, we found only two instances that indicated the presence of a KRAS mutation and STK11 deletion [6,8,9]. We conducted genetic testing on the patient's tissue samples twice, once from the mediastinal mass and once from the supraclavicular metastatic lymph nodes and both results were confirming the presence of the HER2 p.R678Q mutation.To our knowledge, this is the first reported case of HER-2 mutation in mediastinal MAs. HER-2, or Human Epidermal Growth Factor Receptor 2, is a tyrosine kinase receptor that activates the PI3K-AKT-mTOR and RAS-RAF-MEK-ERK pathways, which are more commonly detected in breast cancer [14] and play critical roles in regulating cell growth and transformation [15]. The patients with p.R678Q mutation have demonstrated sensitivity to HER-2 inhibitors, including Trastuzumab, T-DM1, Lapatinib, Pyrotinib, and others [16–18]. Furthermore, the increased frequency of p.R678Q mutations in the second sample indicates molecular progression of the disease and emerges as a potentially superior treatment option for this tumor and MAs with HER2 mutation may befinit from HER2 inhibitors. In our case, we initiated targeted therapy with HER2 inhibitors when the disease had already involved the bone marrow, typically considered a terminal stage with a very poor prognosis. The potential factors contributing to treatment resistance may be missing the optimal timing of administration, in addition to the tumor heterogeneity. Unfortunately, samples from the patient were not enough to conduct molecular profiling and drug sensitivity assays which may deepen our understanding of the disease and treatment resistance mechanisms. Therefore, we speculate that earlier administration of HER-2 inhibitor medication when the patient's general condition is better might lead to a more favorable prognosis. However, the optimal timing and combination of targeted therapy with surgery, chemotherapy, and radiotherapy require further investigation.

4. Conclusion

In conclusion, we reported a rare case of MA in the mediastinum. Throughout the diagnostic and treatment processes, we dedicated our efforts to seeking improved solutions for this uncommon ailment. In addition to conventional treatments, we delved into the application of HER-2 inhibitor medications guided by genetic testing. Most importantly, personalized therapy determined by the results of next-generation sequencing has the potential to yield greater benefits for our patients.

Ethics statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013), and the written informed consent was obtained from the patient.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [Li Lin], upon reasonable request.

CRediT authorship contribution statement

Yu Zhang: Writing – original draft, Investigation, Formal analysis, Data curation. **Jinqiu Rui:** Writing – original draft, Data curation. **Jun Liang:** Writing – review & editing, Data curation. **Li Lin:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation.

Declaration of competing interest

Jinqiu Rui is an employee of Geneplus-Beijing (Beijing, China). The remaining authors report no conflict of interest.

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