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TUMORAL EXTRAMEDULLARY HEMATOPOIESIS IN MEDISTINUM - CASE REPORT AND REVIEW OF RELEVANT DOCUMENTATION

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ABSTRACT

Extramedullary Hematopoiesis (EMH) is the expansion of stem cells, hematopoietic progenitor cells and their differentiation outside the bone marrow. This condition occurs as a compensatory mechanism for the ineffective hematopoiesis of the bone marrow. Pathological EMH is triggered by hematopoietic disorders and other pathological stress conditions, such as infections, malignant tumor, anemia, and metabolic disorders. Pathological EMH has been reported to occur in many organs, and sites of pathological EMH may be involved in reactivation of embryonic hematopoietic structures in these organs. Pathological EMH has been extensively studied in recent years. In particular, pathological EMH caused by end-stage malignancy contributes to tumor immunosuppression. Thus, a deeper understanding of the mechanism of pathological EMH could be beneficial for the development of therapies against tumor development processes.

We report a rare case of an extramedullary hematopoietic tumor in the mediastinum, diagnosed by histopathology, for reference to colleagues.

Keywords: Extramedullary Hematopoiesis*;* Tumoral extramedullary hematopoiesis, Cytology; Histopathology.

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1. INTRODUCTION

Hematopoiesis usually occurs in the bone marrow in adults, and when it occurs at sites other than the bone marrow, it is called extramedullary hematopoiesis (EMH). EMH is commonly found in organs strongly involved in fetal hematopoiesis, including the liver, spleen, and lymph nodes. Other organs and tissues may be involved (heart, thymus, kidneys, adrenal glands, prostate, pleura, skin, fatty tissue, and nerves). Fine-Needle Aspiration Cytology (FNAC) is an easy and fast method for definitive diagnosis of EMH.[1.2.3]

Imaging features, both of common and abnormal anatomical sites, on computed tomography (with contrast) EMH include heterogeneous soft-tissue masses that are poorly perfused and often interspersed with areas containing adipose tissue. Ultrasonography showed that these areas were solid, non-calcified, and vascularized. Using magnetic resonance imaging, EMH appears as heterogeneous signal regions, mainly within fat tissue, hyperintensity both on pre-injection (fat-rich) T1-weighted images and enhanced magnetic contrast enhancement low level. The SPECT technique using Technetium-99m can be helpful in diagnosing EMH: Suspicious areas often show the presence of bone marrow components (Born Marrow-BM) within. Abdominal EMH usually presents as hepatosplenomegaly with or without focal soft tissue areas in the liver, spleen, peritoneum, and peri-adrenal region. The ability of hematopoietic stem and progenitor cells (HSPCs) to migrate away from the BM to adapt and function in extramedullary tissues is complex and is not yet fully understood.[4.5]

Intrathoracic EMH often appears on routine radiographs like a mediastinal tumor but has a relatively large scope and size. Although radiographic features are typical in some cases for the diagnosis of intrathoracic EMH, invasive methods such as bronchoscopy with transbronchial biopsy, guided fine-needle aspiration Ultrasound or CT, CT-guided transthoracic biopsy, endoscopic ultrasound-guided fine-needle aspiration (EBUS), mediastinoscopy, thoracoscopy, endoscopic assisted thoracoscopic surgery video support and thoracotomy are essential for a definitive diagnosis.[3.6]

Typical cytology/histopathological findings of EMH include a full picture of the connective tissue organization including a full range of myeloid cells (medulocytes, post-myelocytosis, choroidal leukocytes, platelets, pre-lymphocytes, lymphocytes...) and no malignant cells were found.[2]

Treatment of EMH is mainly about treating its complications (treatment of symptoms). The methods of curative treatment, supportive treatment currently do not have clear guidelines and there are not many research reports.[7]

2. CASE REPORT

The male patient, 29 years old, was transferred to the National Lung Hospital (NLH) with a diagnosis of mediastinal tumor.

History: Patient was diagnosed with Thalassemia and had splenectomy 10 years ago. About 2 months from the time of admission, the patient showed a cough, cloudy sputum, chest pain, frequent choking, choking when drinking, fatigue, weight loss, poor sleep. The patient came to the health center, took a chest

X-ray and was diagnosed with a lung tumor. The patient was transferred to the provincial pulmonology hospital; Here, the patient was tested chest X-ray filmed, diagnosed to monitor mediastinal tumor (more towards Lymphoma). The patient was then transferred to the NHL. The patient has been vaccinated with 3 doses of the Covid-19 vaccine and has not been infected with this disease.

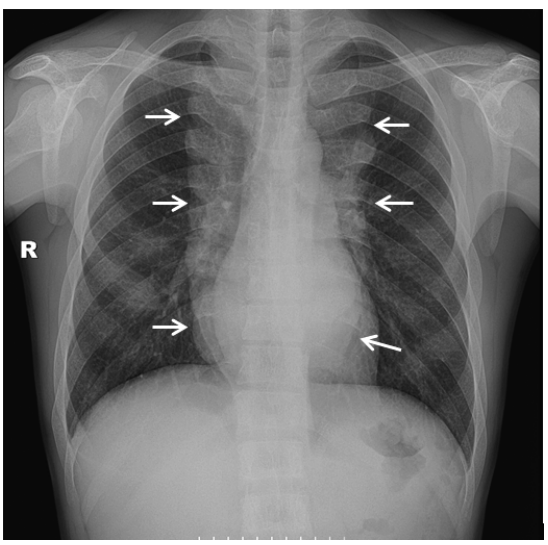
Examination at admission: The patient is awake, has good contact, cough with sputum, mild dyspnea, pale skin and mucous membranes, there are a few enlarged lymph nodes in the posterior region behind the sternocleidomastoid muscle in the left neck. Auscultation of the lungs has few moist rales, liver is not enlarged, spleen (-/removed), peripheral lymph nodes at other sites are not enlarged. The patient's condition was average (BMI 18.4), pulse: 108 beats/min, blood pressure: 100/60 mmHg, weight: 50 kg, height: 165 cm; no edema, no bleeding under the skin. Examination of other organs (cardiovascular, digestive, neurological, musculoskeletal, endocrine...) showed no abnormalities.

The patient had basic laboratory tests (CBC, Blood biochemistry, urine biochemistry, hemostasis, blood gases): the results were within normal limits except for the patient's low hemoglobin (7.5 g/L); Electrocardiogram, echocardiography, general abdominal and urinary ultrasound showed no abnormalities. PCR test Sars – CoV-2: negative.

Tuberculosis tests (AFB sputum, Gene X pert sputum, sputum culture): negative results. Patients undergoing bronchoscopy: Inflammation of the tracheobronchial mucosa; Bronchial mucosal biopsies: Bronchitis.

The patient had a standard chest X-ray film, detailed results are shown in Figure 1.

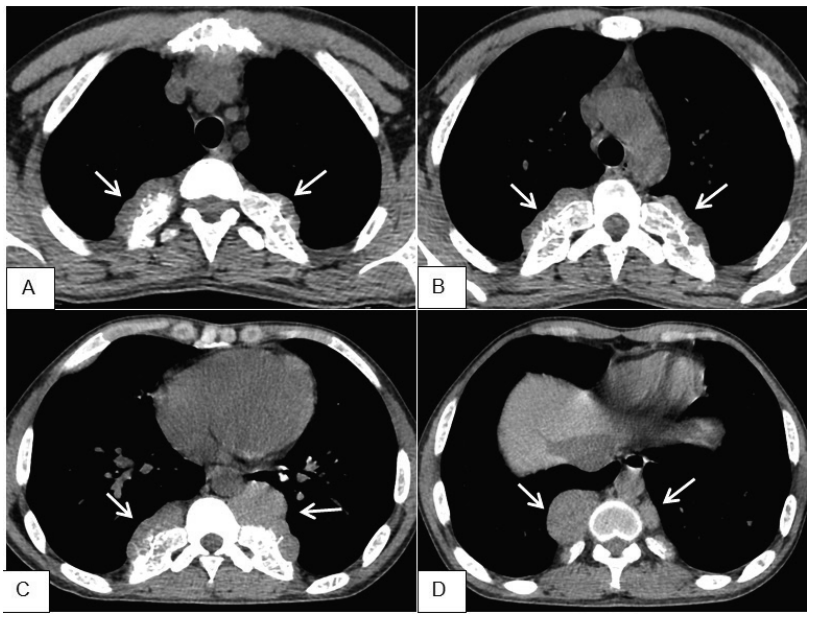
Figure 1. Standard chest X-ray when the patient was admitted to the hospital



Wide mediastinal watermark appears ((upper, middle; (arrows)). The bilateral mediastinal border is clear => the watermark does not belong to the anterior mediastinum. The ends in the posterior arch of the ribs are submerged in the opacity but still observed => may be opacities in the middle mediastinum.

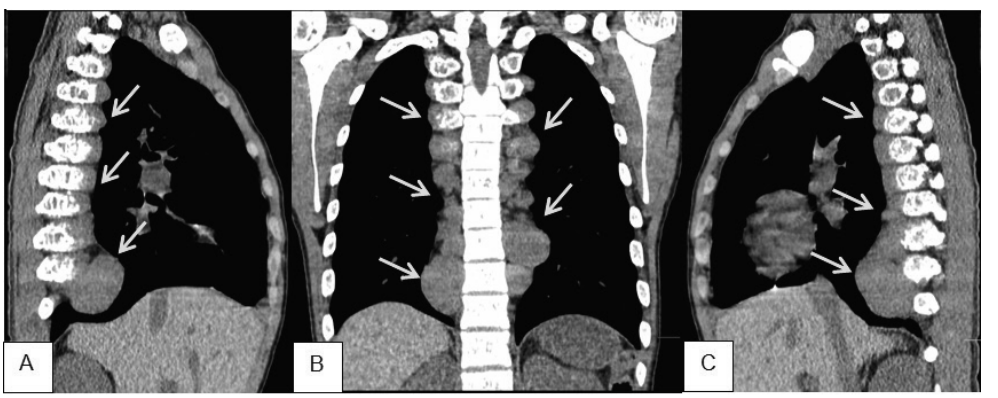
The patient had a chest CT scan, with contrast injection. The detailed results are shown in Figure 2; 3 and 4.

Figure 2. CT chest, mediastinal window, before contrast injection, slices from top to bottom



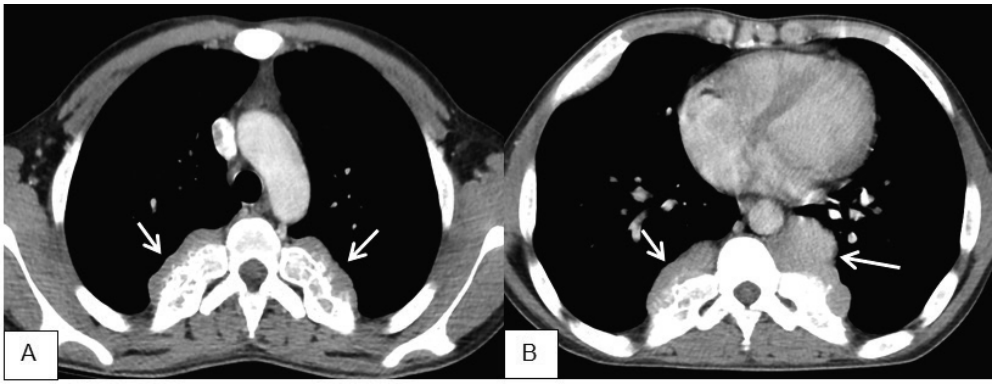
Appearance of soft tissue organization, covering the entire anterior and posterior ends of the ribs. Rib shells lose continuity and smoothness (arrows)

Figure 3. CT chest, mediastinal window, before contrast injection, right Sagital image (A); Coronal through the spine (B) and left Sagital image(C).



Soft tissue organization (#49HU) is nodular, mass, adherent to the vertebral margin and posterior ends of the ribs (arrows) with normal vertebral bodies but the posterior rib heads have heterogeneous bone density best.

Figure 4. CT chest, mediastinal window, after contrast injection, 2 slices from top to bottom



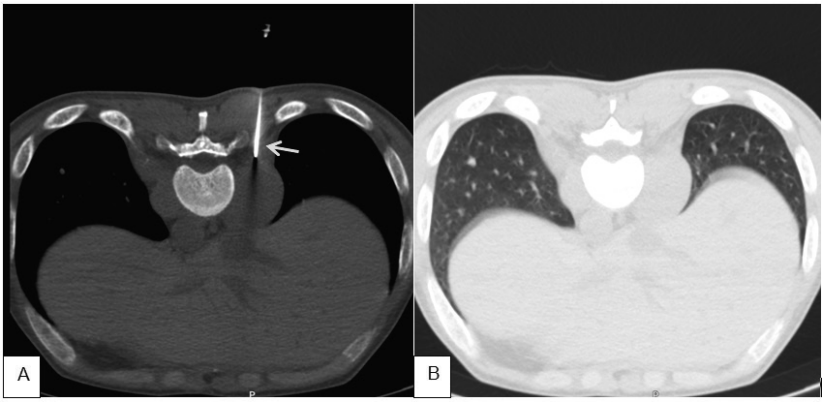
Soft tissue organization as depicted in Figure 3 shows poor contrast enhancement (#52 HU). Spread # 4 HU (not significant).

Chest CT shows 2 possibilities: (1) Lymphoma; (2) Tumor-like abnormalities of extramedullary hematopoietic tissue (EMH). Suggestions: (1) aspiration of left cervical lymph node; (2) Biopsy under the guidance of CT to diagnose MBH.

The patient underwent left cervical lymph node aspiration. The cytological results showed that it was an inflammatory lymph node hyperplasia.

CT-guided transthoracic biopsy was performed. Details are shown in figure 5.

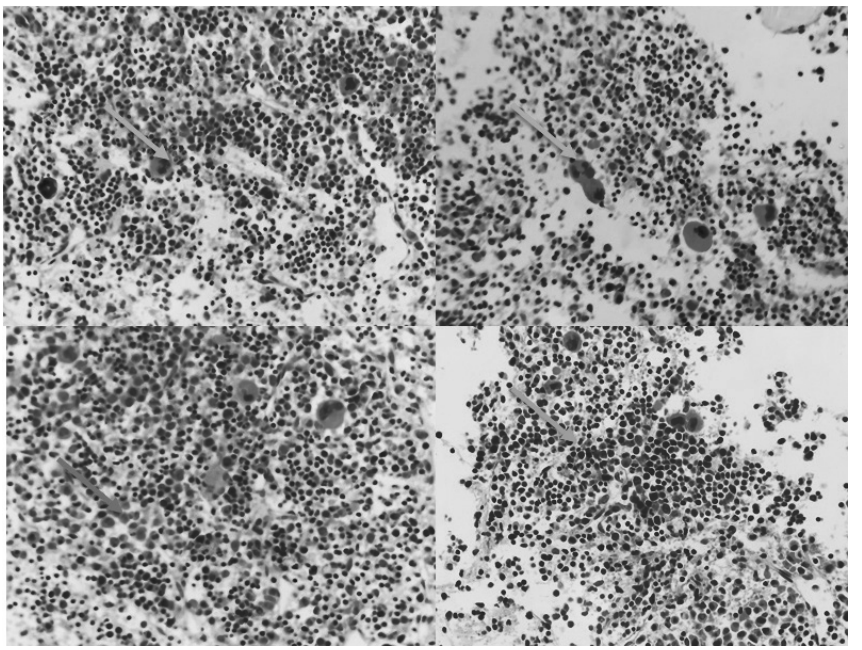
Figure 5. Transthoracic biopsy of tumor tissue under CT guidance



A. The Biopsy needle path (arrow) reaches exactly where the tumor. B: After needle removal, no pneumothorax was seen

***The pathological results of the transthoracic biopsy:** The biopsy piece is a connective tissue that shows all hematopoietic stem cells (myelocytocytes, post-myelocytocytes, choroid leukocytes, polymorphonuclear leukocytes, and platelet prototypes), pre-lymphocytes, lymphocytes), no malignant cells were found. **Conclusion:** Extramedullary hematopoietic tissue in the mediastinum (Extramedullary Hematopoiesis). Details of the HE image are shown in Figure 6.

Figure 6. Microscopic image of the biopsy fragment at 400 magnification



Green arrow: Platelet prototype; Orange arrow: Prelymphocytes, lymphocytes; Red arrow: Myelocytes, postmedullary cells.

*** Final definite diagnosis of the case:** ***Case of extramedullary hematopoietic tumor in the mediastinum/Tumoral extramedullary hematopoiesis in medistinum at thalassemia patient.***

3. DISCUSSION

Hematopoiesis usually occurs in the bone marrow in adults, and when it occurs in sites other than the bone marrow, it is called extramedullary hematopoiesis (EMH) and is commonly found in the organs involved. Strong effects on fetal hematopoiesis, such as liver, spleen, and lymph nodes, may be involved in reactivation of embryonic hematopoietic structures in these organs. It is very rare for EMH to appear in the connective tissue areas adjacent to the spongy bone structure.[1]

Kapatia G et al reported 10 cases of EMH. The mean age of patients was 42.5 years (14 to 78 years). The most common site of EMH was the lymph node (n=8.80%), followed by the paravertebral region (n=2.20%). Only one case of EMH was clinically diagnosed. The patient's mean hemoglobin was 7.9 g/L. Bone marrow analysis was performed in 6 cases. The FNAC showed a different mixture of bone marrow hematopoietic factors including: megakaryocytes (2.6%); Myelocytes and metamyelocytes/neutrophil progenitor cells (29.2%); Erythroid precursors (3.2%,); Polymorphs (21.7%); Blasts (1.1%,); Eosinophils (2.5%); Lymphocytes (39.7%). The histopathology results of our case report are also consistent with this literature.[2]

The most common causative agents of EMH are several chronic hematologic disorders, such as chronic hemolytic anemia, thalassemias, myelofibrosis, atherosclerotic disease, disseminated bone metastatic disease, and lymphoma and leukemia. Other

medical conditions, such as infections or hypermetabolism, can also promote EMH. Further study of the cellular and molecular mechanisms involved in EMH is crucial to prevent its pathological activation. Mobilized peripheral hematopoietic stem and progenitor cells (HSPCs) are considered as key players for EMH generation. HSPCs migrate and establish in the BM as well as in peripheral tissues through binding of CXCR4 to CXCL12. In addition to this CXCR4/CXCL12 axis, other molecules and metabolites are involved in HSPC recruitment and nesting in other organs, such as CSF/Kit, CCL2/CCR2 and sphingosine-1-phosphate (S1P) and its receptor (S1PR) among others. The specific roles of these different axes of EMH have been identified using targeted animal models for these molecules, and it has been suggested that they may contribute to specific diseases; such as the CCL2/CCR2-dependent EMH of the spleen in supporting tumor growth. The case we reported was diagnosed with autoimmune thalassemia (Thalassaemia) 10 years ago and underwent splenectomy. At the same time, postoperative results were good. Progression over time, hemolysis continues, the production of blood cells in the bone marrow cannot fully meet the deficiency, EMH appearing in the connective tissue around cancellous bone is also consistent with the cases. literature reported.[3.4]

EMH can appear in other locations. Chernak BJ et al; Judy BF et al; Ricchi P et al reported cases of EMH occurring in the canal, epidural. Spinal cord compression occurred and was diagnosed preoperatively as epidural tumor or epidural hematoma. The authors recommend that patients with chronic ischemic disease often have the potential to develop EMH and that a definitive diagnosis of this disease before surgery is extremely important and in these cases acute decompression surgery root canal treatment is imperative to avoid severe neurological complications for patients.[5.6.7]

Chiu SC et al conducted NC EMH on experimental animals. Extramedullary hematopoiesis (EMH) is a pathological process secondary to bone marrow failure (BM), EMH reflects an altered relationship between hematopoietic stem and progenitor cells (HSPCs) and their original and new microenvironment. Ability to mobilize hematopoietic stem cells (HSPCs) from bone marrow; Adaptation and functioning in extramedullary tissues are quite complex and far from our current understanding. The molecular basis of EMH can be further elucidated from NC animals after cross comparisons. A deeper understanding of extramedullary hematopoiesis could help expand stem cells in vitro and establish better treatments for patients requiring stem cell transplantation.[8]

EMH can occur in extramedullary sites alone or in association with other lesions. Cho WC et al reported an extremely rare case of EMH in Solitary Fibrous Tumor (SFT) in a 57-year-old female patient discovered incidentally on mammography. The post-operative specimen results indicated the concomitant features of SFT and EMH). Subsequent bone marrow examination revealed a chronic myeloproliferative disorder in this patient.[9]

EMH may present with a persistent, recurrent pleural effusion of unknown cause. Enokida K et al reported the case of a 71-year-old male patient with a previous diagnosis of myelosuppression who was admitted to the hospital with a bilateral pulmonary embolism

that was not associated with heart failure or hypoalbuminemia. The test is assumed to be fluid infiltration and recurrence between courses of treatment. After 1 year, bone scan using Technetium-99m revealed extramedullary hematopoietic tissue on both sides of the thoracic spine. Due to the narrow area of the lesion, it was missed on chest CT. The exact mechanism by which the pleural effusion occurred in this case of EMH is unclear. The author suggested that it may be due to inflammation, due to friction between the EMH lesion and the visceral pleura. However, pleural effusion was repeatedly tested as permeable fluid without any clinical manifestations of inflammation, so the above hypothesis was considered unsatisfactory. The mechanism of pleural effusion due to the presence of ascites in the presence of EMH in the liver and other abdominal organs has also been reported. In these cases, ascites may be associated with portal hypertension (present in 10-20% of cases with myeloproliferative disorders) due to increased portal blood flow and portal vein thrombosis. Although detailed evaluation of portal hypertension was not performed in this case, abdominal CT showed an irregular liver surface and liver margins suggestive of cirrhosis. Bone marrow scintigraphy showed the presence of EMH in the liver. Therefore, the etiology of pleural effusion similar to the mechanism of intra-abdominal ascites is also posited, but there is no satisfactory answer.[10]

Extramedullary hematopoiesis is related to the thyroid gland. Jan IS et al conducted study of 63,361 thyroid FNA samples in Taiwan from January 2000 to December 2016. The results detected 4 cases of EMH in the goiter. These four female patients presented with nodular goiter and hematopoietic factor foci without any chronic hematopoietic tissue disease or any evidence of thyroid malignancy.[11]

Extramedullary hematopoiesis (EMH) can occur in the liver and is generally considered pathological in adults. Tremblay D et al reported reviewing 42 liver biopsies with EMH and developed a new classification system to quantify EMH levels from 1 to 3. Reusltts: 17 patients had hematologic disease, which is common. especially myeloproliferative cancers (n = 9). Patients with underlying hematological disease had a significantly higher EMH index than patients without this condition (P < .0001). All patients with grade 3 EMH had a definitive diagnosis of hematologic disease; and most patients with grade 1 EMH (86%) present with myelodysplasia. Conclusion: The data suggest that grading of EMH in the liver is feasible and can identify patients who may have an underlying hematologic pathology that can guide further diagnosis[12].

4. CONCLUSION

Extramedullary hematopoiesis is a condition that can occur in individuals with hematopoietic diseases, especially when bone marrow hematopoiesis is not sufficient to compensate for anemia. EMH can occur at any anatomical site in the body but is most commonly found in organs strongly involved in hematopoiesis during fetal life such as the liver, spleen, and lymph nodes. Our case report EMH appearing in the connective tissue around the cancellous bone (ribs, spine) is a rare condition, creating images of mediastinal tumors that are difficult to diagnose on film. Our desire is for doctors to update this rare case so that there will be a better diagnostic approach when encountering similar cases.

ETHICAL APRROVAL

All producers performed in studies involving human participants were in accordance with the standards of the NLH Ethics Board and with the 1964 declaration of Helsinki and subsequent amendments, or equivalent ethical standards.

CONSENT FOR PUBLICATION

The patient received informed writen informed consent for release of clinical detail. However, in the article the identity of the patient was hidden.

DISCLOSURE

The author report no conflicts of interest for this work.

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