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CASE REPORT

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Angiosarcoma of the lungs, liver, and bones in a 27-year-old male patient

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ABSTRACT

Angiosarcoma is a rare (from 1% to 2% of all soft tissue sarcomas), highly aggressive endothelial tumor that may affect any organ. The prognosis for the disease is poor, particularly if it is metastatic by the time of diagnosis. The etiology is unclear; however, there are definite risk factors including chronic lymphedema, radiation therapy, familial syndromes, and exposure to environmental chemical toxins and foreign bodies. Although the final diagnosis is histopathological, radiological tools such as ultrasound, CT, and MRI are still necessary to determine the stage of cancer. Treatment includes surgery, chemotherapy, and radiation therapy. Chemotherapy is the main treatment strategy for metastatic angiosarcoma, however, the toxicity level of frequently used agents is high. The research focuses on targeted medicines and immunotherapy as potential therapeutic options. We present a case of angiosarcoma in a young man without chronic illnesses with metastatic spread to the lungs, liver, and bones at the time of diagnosis.

Key words: angiosarcoma, metastases, etiology, diagnostic tools, treatment, prognosis

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Introduction

Angiosarcoma is a malignant and aggressive tumor of vascular or lymphatic origin. Angiosarcoma can develop in any organ of the body [1]. The cutaneous form is the most common (50%), with the head and neck as the most frequently involved region [2]. Only 10% of all angiosarcomas occur in deep soft tissues (the extremities, peritoneum, retroperitoneum, and the body wall), and the rest are found in organs such as the breast, heart, lungs, bone, spleen, liver, kidneys, and testes [3]. Regardless of its site of origin, angiosarcoma has a high tendency for metastatic multifocal disease. The lungs are the most frequent site for metastases [4]. Other frequent sites include the liver, bones, and lymph nodes [5]. At diagnosis, multiorgan involvement usually occurs, often rendering it difficult to establish the site of origin.

Angiosarcoma is one of the rarest types of adult soft tissue sarcomas, accounting for about 1–2% of all sarcomas [1]. In Europe, the crude incidence rate is around 0.31/100,000/year [6]. It can occur at any age. However, it is more common in older individuals, with a reported median age between 60 and 71 years [7]. There is generally no gender predilection, except for cutaneous lesions, which are more prevalent among males [8].

The etiology is unknown, although there are definite risk factors that have been identified for angiosarcoma. The two most common ones are chronic lymphedema [9] and radiation therapy [10]. Angiosarcoma also has a genetic predisposition associated with familial syndromes, such as Recklinghausen neurofibromatosis, xeroderma pigmentosa, Klippel-Trénaunay syndrome, bilateral retinoblastoma, hemochromatosis, Maffucci syndrome, and Ollier disease [1]. Other risk factors include exposure to environmental chemical toxins (arsenic, vinyl chloride, anabolic steroids) [11], foreign bodies (synthetic materials used in grafts or prostheses) [12], and prior trauma or surgery [13].

Angiosarcoma can be detected on ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI); however, it is usually difficult to distinguish it from other cancer types [7, 14]. Biopsy, pathology

tests, and immunohistochemical analysis are required to confirm the diagnosis [15].

The treatment options include surgery, chemotherapy, and radiotherapy, usually with all three combined [1]. Angiosarcoma is often diagnosed at an advanced stage, and the prognosis is generally poor. Overall survival ranges anywhere from 6 to 16 months. It is even worse in cardiac or liver angiosarcoma, where the prognosis is less than 3 months [3].

We present a case of angiosarcoma in a young man without chronic illnesses with metastatic spread to the lungs, liver, and bones at the time of diagnosis.

Case report

A 27-year-old male patient was admitted to the Department of Internal Medicine, Diabetology and Clinical Pharmacology of the Medical University of Lodz, Poland, due to progressive weakness; impaired exercise tolerance; drowsiness; easy bruising; bleeding from the nose and mouth; edema of the right lower limb; and pain in the body of various locations, such as the right part of the chest, the left part of corpus, and the lumbar-sacral area of the back. The presented symptoms had gradually increased over the previous month. The patient also reported a lack of appetite and loss of weight (four kilograms in a month).

The patient's medical history included information on a condition following a traffic accident with a secondary concussion, pulmonary contusion, a crush injury to the left lower limb and transfemoral amputation of the extremity, a fracture of the right arm, and removal of the spleen in 2015. Additionally, the patient suffered a fracture of the left humerus in 2020. He denied the presence of chronic diseases or taking medications regularly.

On admission, the patient was alert and co-operative. Physical examination revealed bruises on the skin. Due to excessive nose bleeding, insertion of anterior tamponade was required. The body temperature was 36.6°C; the pulse rate was 80 beats per minute, and the arterial blood pressure was 120/70 mmHg. The breath and cardiac sounds were normal. The abdomen was soft and painless, the liver was impalpable, peristalsis was audible, and peritoneal signs were absent. Goldflam's sign was negative on both sides. Edema of the right lower limb was observed. A digital rectal examination showed brown stool, without blood or sputum. The testes were of normal size, painless, and without palpable tumors.

An electrocardiogram indicated steady sinus rhythm, 100 beats per minute, a normal axis, and without ischemic features.

The laboratory tests revealed abnormalities: red blood cells (RBC) 2.94*10 ^ 6/μL (reference values 4.20–6.10), hemoglobin level (HGB) 11 g/dL (14.0–18.0), hematocrit (HCT) 31.4% (40.0–55.0), mean corpuscular volume (MCV) 107 fL (80–98), platelet level (PLT) 52*10 ^ 3/L (150–400), aspartate aminotransferase (AST) 53.9 U/L (0.9–50.0), alkaline phosphatase (ALP) 139.7 U/L (30.0–120.0), gamma-glutamyl transpeptidase (GGTP) 277.1 U/L (< 55.0), total bilirubin 49.8 umol/L (5.0–21.0), D-dimer > 80 mg/L (< 0.5), C-reactive protein (CRP) 16.1 mg/dL (< 0.5), sedimentation rate (SR) 12 mm/1h (< 8), and lactate dehydrogenase (LDH) 250.5 U/L (< 240). The tumor markers — carcino-embryonic antigen (CEA), cancer antigen 19–9 (CA 19–9), α-fetoprotein (AFP), and prostate — specific antigen (PSA) — were negative. The panel of antibodies against Epstein-Barr virus (EBV), cytomegalovirus (CMV), *hepatitis B virus* (HBV), *hepatitis C virus* (HCV), and human immunodeficiency virus (HIV) was negative.

A chest X-ray examination showed no abnormalities. However, ultrasound examination of the abdomen revealed a slightly enlarged (craniocaudal length 150 mm) heterogenous liver with a large area of hyperechoic infiltration in the left lobe and numerous hyperechoic lesions up to 30 mm in diameter (Fig. 1a, 1b).

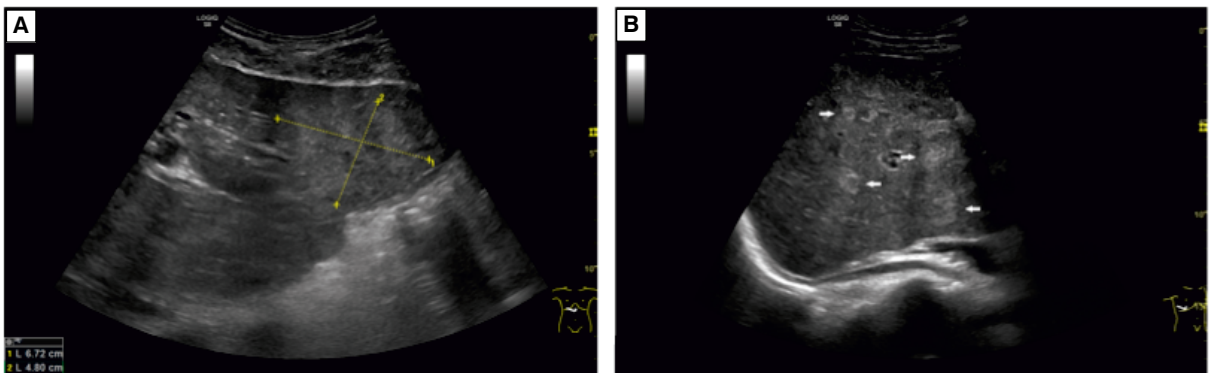

Figure 1. A. Ultrasound image of a large hyperechoic lesion in the left lobe (marked and measured); **B.** ultrasound image of hyperechoic lesions in the liver (the largest ones marked with white arrows)

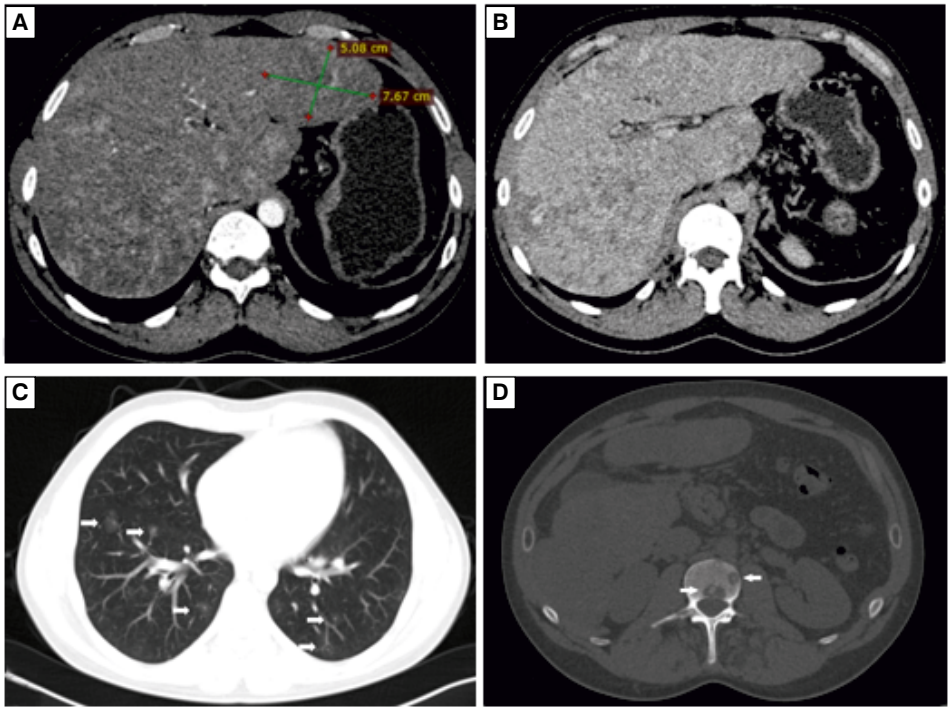

Figure 2. A. CT image of a lesion in the left liver lobe marked and measured, arterial phase; **B.** CT image of diffuse liver infiltration with numerous small nodules, venous phase; **C.** CT image of metastases to the lungs; **D.** CT image of metastases to the vertebrae

A CT scan of the chest and the abdomen was performed. CT examination confirmed a large pathological mass in the left liver lobe (Fig. 2a) infiltration of the liver with heterogenous contrast enhancement, and small-nodular remodeling (Fig. 2b). In both lungs, numerous scattered, confluent, ground-glass metastatic lesions with a central solid part were found (Fig. 2c). In addition, lytic metastatic remodeling of the skeleton was found in many sites, such as vertebral bodies (Fig. 2d), the sternum, ribs, and both hip bones.

A bone marrow-originated hematological disease was suspected; however, it was excluded in a bone marrow biopsy. Next, an ultrasound-guided core-needle biopsy of the liver lesions was performed. Microscopic examination revealed a disseminated infiltration of branching vascular structures, clusters, and bands of slightly spindle-shaped cells indicating a malignant proliferation of vascular origin (Fig. 3a). The vascular differentiation of the malignant cells was confirmed in immunohistochemistry using anti-CD31 (Fig. 3b), and anti-CD34 (Fig. 3c) antibodies, which were positive in the neoplastic cells. Broad-spectrum cytokeratins (CKAE1/AE3), cytokeratin 7, and 19 (CK7 and CK19) were positive in the preexisting bile ducts (Fig. 3d). Cytokeratin 20 (CK20) and CDX2 were negative in neoplastic cells and the bile ducts. Ki67 proliferation index was increased — by approximately 20%, reaching 35% in hot spots (Fig. 3e). Based on the microscopic and immunohistochemical features, low-grade angiosarcoma was diagnosed.

During the patient's hospitalization, due to thrombocytopenia and recurrent nose bleedings, the patient required platelet transfusion and the administration of tranexamic acid and etamsylate. Because of severe and aggravating pain, the patient needed anesthetics such as tramadol with paracetamol, metamizole, and hydrocortisone. He responded well to the treatment. The patient was referred to an oncologist and qualified for chemotherapy with paclitaxel. He received one course of chemotherapy. Complications appeared, such as disseminated intravascular coagulation, bleedings, and severe infection. Symptoms were a consequence of the disease rather than the treatment. Unfortunately, the patient died two months after his first admission to the hospital, including three weeks of diagnostics and five weeks of therapy.

Patients consent: Written informed consent has been obtained from the patient to publish this paper.

Discussion

The unique feature of this report concerns the young age of the patient at the diagnosis of angiosarcoma. The

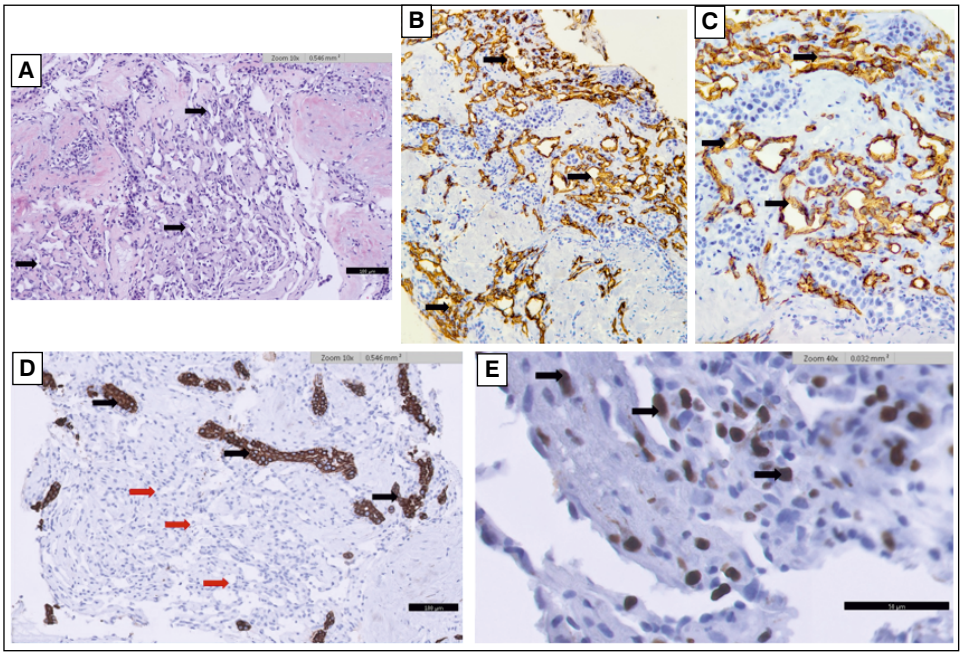

Figure 3. A. Histopathological image of the neoplastic vascular proliferation with clusters and bands of spindle-shaped cells (black arrows) in H&E (haematoxylin-eosin) staining. Magnification of 10×; **B.** Immunohistochemical staining revealing positivity for CD31 in the neoplastic cells (black arrows). Magnification of 10×; **C.** Immunohistochemical staining revealing positivity for CD34 in the neoplastic cells (black arrows). Magnification of 10×; **D.** Immunohistochemical staining for CKAE/AE3 revealing negativity for cytokeratins in the neoplastic cells (red arrows) and positivity in preexisting bile ducts (black arrows). Magnification of 10×; **E.** Immunohistochemistry for Ki67 revealing increased proliferation index in hot-spot (35%, black arrows indicating positive cells). Magnification of 40×

literature describes 60–70 years as the usual age for developing advanced angiosarcoma [7]. There are no available data on whether a younger age at the time of diagnosis is associated with a more aggressive course of the illness.

Our patient did not suffer from any comorbidities or have a history of chronic lymphedema, radiotherapy, familial syndromes, exposure to environmental chemical toxins, or foreign bodies. The only aspect considered a potential triggering factor was a major, general stress reaction following the described traffic accident, which resulted in the loss of the left lower limb.

At the time of diagnosis, the angiosarcoma infiltrations were found in many sites. Therefore, it is difficult to ascertain the site of origin. We cannot exclude that the primary cancer site was somewhere in post-traumatic areas. Some studies have documented developing angiosarcoma in the shoulder after trauma [13] or around total hip arthroplasty [12].

Furthermore, in our paper, we thoroughly described ultrasonography and tomography documentation on the changes in the lungs, liver, and bones. It is a unique description of angiosarcoma in various, distant sites of the skeletal system, e.g., the sternum, ribs, and both hips. There are only a few studies with a radiological presentation of metastatic angiosarcoma in the bones, mainly in the skull [16] and limbs [17].

The diagnosis of angiosarcoma is mainly based on histological criteria, followed by immunohistochemical studies. Several entities must be excluded during differential diagnosis (including both benign or other malignant vascular neoplasms such as hemangiomas or epithelioid haemangioendothelioma, as well as tumors of other differentiation including most of all carcinomas and carcinosarcomas) [18]. In our case, the neoplastic cells revealed malignant morphological features and unequivocal vascular differentiation in immunohistochemistry (positivity for CD31, and CD34, and negativity for cytokeratins). In summary, in each case suspected of angiosarcoma, it is necessary to collect a biopsy as soon as possible. However, histopathological diagnosis of angiosarcoma is still a great challenge because of the rarity of occurrence and changes in the histological classifications of sarcomas [19].

Moreover, treatment options include surgical excision with wide margins, chemotherapy, and radiotherapy. Surgical resection is the primary treatment of choice and remains the most effective option [20]. Unfortunately, it was impossible to a perform surgical procedure on the patient because of multi-located changes.

Adjuvant chemotherapy brings limited benefits to patients after surgery or radiotherapy [20]. However, chemotherapy is the treatment of choice for metastatic angiosarcoma [21]. The most commonly used chemotherapy agents include taxanes (paclitaxel and docetaxel), doxorubicin, liposome doxorubicin, and ifosfamide [22]. In many patients with angiosarcoma, the use of chemotherapy is limited by the patient's advanced age, comorbidities, and the risk of drug-related toxicity.

Out of the numerous pro-angiogenic factors, vascular endothelial growth factor (VEGF) could be of major importance in future angiosarcoma management. There are in vitro research and small clinical trials using VEGF-targeting agents. The treatment results are promising; however, further investigations are required [23]. Moreover, immunotherapy opens a new chapter of therapeutic options. The first results of small-cohort trials on the treatment of metastatic or unresectable angiosarcomas with ipilimumab and nivolumab are promising [24]. Both molecules require further investigation.

There are no observation trials that can confirm whether radiation therapy alone is effective for angiosarcomas. Some retrospective studies show that adjuvant radiotherapy following radical surgery is an optimal treatment combination and improves overall survival [25].

Finally, angiosarcoma is often diagnosed at an advanced stage, and it is associated with a poor prognosis. The reported 5-year survival rates range from 12% to 35% [26]. Outcomes vary considerably and are dependent on the site, size, resectability, tumor type, and presence of metastases. In the analyzed case, the multi-site location of the changes at the time of diagnosis, involvement of key organs, and non-resectable type of the tumor from the very beginning were associated with a worse prognosis for the patient.

Conclusions

Continuous medical education and analysis of rare soft tissue neoplasms and close collaboration between physicians, radiologists, and pathologists are crucial for early diagnosis and initiation of the treatment. Further studies focused on targeted medicines and immunotherapy are required to develop effective therapies for angiosarcoma.

Conflicts of interest: *None.*

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