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Angiosarcoma of the caecum

Ангиосарком цекума

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SUMMARY

Introduction Primary angiosarcomas arising from the digestive system are rare, representing less than 1% percent of the malignant sarcomas. Only a few cases have been reported in the literature. Colorectal involvement is exceedingly uncommon and is a harbinger of a poor prognosis with widespread metastasis. Diagnosis is often delayed due to non-specific symptoms and pathology which mimics other tumors.

Case outline In our case, a 52-year-old woman presented to the emergency room in the middle of July 2021, complaining of protracted malaise, and rapid fatigue and occasional sweating. MSCT of the abdomen and small pelvis revealed the existence of lobular, well vascularized, heterodensal lesion, located supravesically along the anterior contour of the uterine corpus, in the convolutes of the small intestine. Patient was subjected to operative treatment with curative intent. Intraoperatively, a completely tumor-altered caecum was verified. Standard histopathological examination demonstrated a high grade epitheloid angiosarcoma with severe pleomorphism and solid growth pattern. The control MSCT of abdomen and small pelvis which was done 12 months after the operation did not show the existence of any pathological lesions.

Conclusion Both clinical and pathological diagnoses of colorectal angiosarcoma are challenging. Patients are presented with nonspecific symptoms, which can lead to mismanagement and late diagnosis. A pathological diagnosis relies on immunohistochemical staining for endothelial markers. In limited tissue biopsies, it can be easily misdiagnosed as poorly differentiated adenocarcinoma or gastrointestinal stromal tumor. For now, surgical treatment with R0 resection seems to be the only effective treatment modality.

Keywords: angiosarcoma; caecum; gastrointestinal angiosarcoma; colonic angiosarcoma

САЖЕТАК

Увод Примарни ангиосаркоми дигестивног система су ретки, чинећи 1% свих малигних саркома. Само је неколицина случајева описана у литературе. Захваћеност колоректума је изузетно ретка и знак је лоше прогнозе због обично већ постојећих удаљених промена. Дијагноза се обично касно поставља због неспецифичних симптома и патолошких налаза који могу имитирати друге туморе.

Приказ болесника У нашем случају, жена старости 52 године се јавила на преглед због протраховане малаксалости, брзог умарања и повременог презнојавања. Мултислајсни скен абдомена је показао постојање лобуларне, добро васкуларизоване лезије локализоване суправезикално уз редњи зид утеруса, унутар конволута танког црева. Пацијенткиња је оперисана, при чему је верификован у потпуности туморски измењен цекум. Хистопатолошки налаз је потврдио да се ради о ангиоссаркому високог градуса. Контролни мултислајсни скен абдомена и мале карлице, спроведен након 12 месеца није показао постојање патолошких лезија.

Закључак И клиничка и хистопатолошка дијагностика ангиосаркома колоректума су изазовне. Пацијенти се презентују неспецифичних симптомима што може водити ка постављању погрешне дијагнозе. Хистопатолошка дијагностика се ослања на имнохистохемијско бојење на ендотелне маркере, због чега се у појединим условима налаз може погрешно протумачити као слабо диферентоване аденокарциноми ли гастроинтестинал стромал тумор. За сад, хируршко лечење остаје једини ефикасни модалитет у третману.

Кључне речи: ангиосарком; цекум; гастроинтестинални ангиосарком; ангиосарком колона

INTRODUCTION

Primary angiosarcomas arising from the digestive system are rare, representing less than 1% percent of the malignant sarcomas [1]. They usually arise in the stomach and small intestine [2], while colorectal involvement is extremely uncommon and is a harbinger of a poor

prognosis with diffuse metastasis [1, 3]. Diagnosis is often delayed due to non-specific symptoms, but also due to pathology which mimics other tumors. Management guidelines are very limited due to tumors rarity.

CASE REPORT

A 52-year-old woman presented to the emergency room in the middle of July 2021, complaining of protracted malaise, and rapid fatigue and occasional sweating. No other difficulties were listed. The patient was a diabetic with a significant medical history and was hospitalized several times in our Institution, last time 3 years ago due to myocardial infarction and transient ischemic attack. Since then, the patient has been diagnosed with ischemic heart disease and had been using oral anticoagulant therapy regularly due to the presence of echosonographically verified thrombus in the apical area of the heart. Also, two years ago she was examined on an outpatient basis by a hematologist in order to perform tests for thrombophilia – genetic analysis on MTFHR, FII and FV Leiden was negative, and homocysteine was in the reference range. She was instructed to conduct tests for antiphospholipid syndrome, which was not done. The family history was positive for malignancies – both parents had liver cancer.

On examination she was slightly hypotensive (90/50mmHg), tachycardic (110/min) with normal body temperature of 36.8°C. Abdomen was slightly distended with hyperactive bowel sounds and without any tenderness. The initial blood analysis revealed leukocytosis with “left shift”, eosinophilia, moderate to severe microcytic anemia and thrombocytosis (Le 51.6; Neu 40.80*10^9/L; Eo 8.60*10^9/L; Er 3.60; Hgb 84; Hct 0.282; Tr 642). Inflammatory parameters were elevated (SE 100/1h, CRP 225mg/L, PSP 1418pg/mL, PCT 0.81ng/mL). Prothrombin time was prolonged (INR 10.64s) but considered as a consequence of an inadequate dose of

warfarin. Urin analysis were normal. Abdominal ultrasound and plain abdominal radiography were without any pathological finding.

The patient was hospitalized on the hematology department for further diagnosis and treatment. Due to the positive inflammatory syndrome, antibiotic therapy was administered empirically and prolonged prothrombin time was corrected. Bone marrow aspiration and trepanobiopsy were performed and the pathohistological finding was without signs of myeloproliferative and lymphoproliferative disease. The origin of eosinophilia was then investigated. X-ray of the paranasal cavities and ENT examination excluded the existence of nasal polyposis. Stool was negative for parasites and to rule out Churg Strauss syndrome, samples were sent for immunology (ANA, pANCA) which came back normal. Esophagogastrodudenoscopy was performed and there were no macroscopic findings to indicate eosinophilic gastritis, as well as the existence of erosions, ulcerations nor neoformations. Chest CT did not show the existence of any changes that would indicate granulomatous inflammation. The IgE immunoglobulin titer was in the reference range.

On the sixth day after admission, the patient had a fever for the first time, accompanied by an increase in leukocyte count and inflammatory parameters (Leu 77.1, CRP 236mg/L). Blood cultures and other bacteriological analyzes, that were taken on several occasions, were sterile. MSCT of the abdomen and small pelvis was performed and showed the existence of lobular, well vascularized, heterodensal lesion measuring around 7x5x8cm, located supravesically along the anterior contour of the uterine corpus, in the convolutes of the small intestine, with hypodense zones in the center which differentially diagnostically corresponded to necrosis. She was examined by a gynecologist, and it was determined that the lesion did not belong to the internal genital organs.

Given the above, the patient was transferred to the Department of General Surgery with the intention of performing explorative laparotomy and further surgical procedure according to

the intraoperative finding. Intraoperatively, a completely tumor-altered caecum was verified with partially necrotic walls and multiple abscesses within them. (Figure 1) Further exploration did not reveal lesions suggestive of secondary deposits. Given the above, a resection was performed (Figures 3-5) along with local lymphadenectomy and reconstruction in a form right hemicolectomy with ileo-transverso T-L anastomosis. Standard histopathological examination demonstrated a high grade epitheloid angiosarcoma with severe pleomorphism and solid growth pattern. (Figure 2). R0-resection was verified and the presence of tumor tissue was confirmed in 0 out of 7 dissected lymph nodes. Patient was staged as $T_2N_0M_x$.

The postoperative period was marked by ventricular fibrillation on fifth postoperative day. The patient was resuscitated and returned to sinus rhythm using DC shock. The rest of the hospitalization was uneventful and after seven days patient was discharged. No evidence of complications was noted during first two controls. The control MSCT of abdomen and small pelvis which was done 12 months after the operation did not show the existence of any pathological lesions.

DISCUSSION

Angiosarcoma is an aggressive tumor that arises from vascular endothelial cells. It accounts for 1% of all sarcomas and 0.001% of all colorectal malignancies [4]. It can be primary or secondary (metastatic). Roughly 60% primary occur in the skin and superficial soft tissue, but may also occur in deep soft tissue and parenchymal organs such as the breast, heart, liver, spleen and bone.

Only a few angiosarcomas have been found in the digestive system, with most of them localized in the stomach and small intestine [2]. Colorectal angiosarcoma is a very rare finding. The first case was described in 1949 by Steiner and Palmer [5], and to our knowledge there were less than 40 described cases to this day, most of which were primary [1, 6, 7]. The

prognosis is poor as the tumor metastasizes rapidly in more than 70% of cases [1]. The most common sites of metastatic disease are lymph nodes, liver, bone and lungs, while other localizations are less represented [8].

The etiology of colorectal angiosarcoma is yet unclear. It may be related to long-term exposure to radiation, chemical agents such as polyvinylchloride, thorotrast and arsenic, as well as a consequence of chronic lymphedema and amyloidosis [9, 10, 11]. Angiosarcoma has also been reported in association with implanted foreign material such as vascular (Dacron) grafts and orthopedic joint prostheses [12, 13, 14], breast implants [15, 16], or in patients with arteriovenous fistulas. [12, 13, 17] According to the findings of recent studies, protracted use of calcium channel blockers may lead to colorectal angiosarcoma [1]. The patient from our report was using calcium channel blockers.

In 2018, Wang et al. summarized the results of 33 previously reported cases [1]. The mean age of patients was 56 years (16 to 85 years) and the mean tumor size was 5cm (1.5–12 cm) [1]. The majority of patients (61%) were female [18]. Most reported colorectal angiosarcomas have been localized to the sigmoid colon [1, 6, 7]. Wang reported that sigmoid colon was affected in 36% of cases, rectum in 33%, cecum in 21% of cases, ascending colon in 9% and the transverse and descending colon in 3% of cases [1]. Before him, Brown et al. had similar results [18]. The most common symptoms are gastrointestinal bleeding and abdominal or perianal pain [6, 7, 19]. Patients may also have symptoms of bowel obstruction and weight loss [6, 7]. Anemia was present in 42% of patients [6, 19]. Our patient had only moderate to severe microcytic anemia.

Patients can be easily misdiagnosed. On endoscopy, the mucosa may look normal or show hypervascularization. It may demonstrate an ulcerated or hemorrhagic, protuberant, near-circumferential mass lesion [8, 20, 21]. Due to aggressive nature and non-specific symptoms, routine screening colonoscopies may be insufficient for timely assessment of these tumors, and

the diagnosis is usually delayed in almost third of the cases [22]. On microscopy, in limited tissue biopsies, angiosarcomas may mimic poorly differentiated carcinomas, gastrointestinal stromal tumor, leiomyosarcomas, melanomas and sarcomas with epithelioid morphology [21, 23].

Due to its rarity, there are no specific guidelines for the diagnosis or the management, and its high aggressiveness prevents designing an optimal therapeutic approach [1]. Patients with angiosarcoma generally have a poor prognosis, but for now surgical treatment with R0 resection seems to be the only effective treatment modality. Wide margins are recommended because of the often-multifocal nature of angiosarcoma and its invasiveness [6, 22].

The long-term outcomes of adjuvant chemotherapy and radiotherapy remain unclear [1, 22, 24]. Komorowski reported a case involving a 19-year-old patient, who was operated on and later received adjuvant chemotherapy and radiotherapy [25]. After 18 months follow-up, the patient had no signs of recurrence [25].

Tumor size and age at presentation have been suggested as prognostic factors that affect the course after treatment and overall survival. Better survival has been associated with tumors which are less than 5cm, as the size has shown to be an independent prognostic factor. [18].

Our patient had a tumor measuring nearly 8cm and was without macroscopically visible secondary deposits. Also, tumor was not found in any of dissected lymph nodes. The control MSCT of abdomen and small pelvis which was done 12 months after the operation did not show the existence of any pathological lesions.

In conclusion, we can say that both clinical and pathological diagnoses of colorectal angiosarcoma are challenging. Patients are presenting with nonspecific symptoms, which can lead to mismanagement and late diagnosis. A pathohistological diagnosis relies on immunohistochemical staining for endothelial markers. In limited tissue biopsies, it can be

easily misdiagnosed. For now, surgical treatment with R0 resection seems to be the only effective treatment modality.

Ethical standards: We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines. Written consent to publish all shown material was obtained from patient.

Conflict of interest: None declared.

REFERENCES

1. Wang Q, Zhao T, Mi BT, Zhang YL, Wei R, Tong HL, et al. Primary Colonic Angiosarcoma Seen in a Patient on Calcium Channel Blocker: A Case Report with Summary Analysis of 32 Other Cases from the Literature. Am J Case Rep. 2018;19:254–61. DOI: 10.12659/AJCR.907287
2. Chen YW, Dong J, Chen WY, Dai YN. Multifocal gastrointestinal epithelioid angiosarcomas diagnosed by endoscopic mucosal resection: A case report. World Journal of Gastroenterology. 2020;26(29):4372. DOI: 10.3748/WJG.V26.I29.4372
3. Jehangir A, Le. BH, Shogbesan O. Angiosarcoma of the Colon Presenting with Chronic Diarrhea, Rectal Bleeding, and Pelvic Discomfort. Cureus. 2017;9(3). DOI: 10.7759/CUREUS.1117
4. al Beteddini OS, Brenez D, Firket C, Algaba R, Tabech A. Colonic angiosarcoma: A case report and review of literature. Int J Surg Case Rep. 2013;4(2):208–11. DOI: 10.1016/J.IJSCR.2012.11.021
5. Steiner CA, Palmer LH. Angiosarcoma of the Colon: With Case Report. Ann Surg. 1949;129(4):538–42. DOI: 10.1097/00000658-194904000-00015
6. Radić S, Zovak M, Marić AG, Baturina S, Kirigin MS, Krušlin B. Multiple Primary Angiosarcomas of the Colon. Case Reports in Pathology. 2021;2021:1–5. DOI: 10.1155/2021/7237379
7. Ottaiano A, Santorsola M, Perri F, Pace U, Marra B, Correra M, et al. Clinical and Molecular Characteristics of Rare Malignant Tumors of Colon and Rectum. Biology (Basel). 2022;11(2). DOI: 10.3390/BIOLOGY11020267
8. Sherid M, Sifuentes H, Brasky J, Shah DA, Ehrenpreis ED. Clinical and endoscopic features of angiosarcoma of the colon: two case reports and a review of the literature. J Gastrointest Cancer. 2013;44(1):12–21. DOI: 10.1007/S12029-012-9431-0
9. Mundt KA, Dell LD, Crawford L, Gallagher AE. Quantitative estimated exposure to vinyl chloride and risk of angiosarcoma of the liver and hepatocellular cancer in the US industry-wide vinyl chloride cohort: mortality update through 2013. Occup Environ Med. 2017;74(10):709–16. DOI: 10.1136/OEMED-2016-104051
10. Tripke V, Heinrich S, Huber T, Mittler J, Hoppe-Lotichius M, Straub BK, et al. Surgical therapy of primary hepatic angiosarcoma. BMC Surgery. 2019;19(1). DOI: 10.1186/S12893-018-0465-5
11. Said S, Graham RP, Wu T-T, Yasir S, Zhang L, Folpe AL. Colonic Angiosarcoma Arising in Association with Amyloid Deposits. Case Rep Gastrointest Med. 2020;2020:1–6. DOI: 10.1155/2020/3780763
12. Takamura K, Kobayash H, Rubin BP, Kondo S, Asami F, Aoyagi R, et al. Aortic Angiosarcoma in Association with Endovascular Aneurysm Repair: Case Report and Review of the Literature. Am J Case Rep. 2021;22(1). DOI: 10.12659/AJCR.931740
13. Agaimy A, Ben-Izhak O, Lorey T, Scharpf M, Rubin BP. Angiosarcoma arising in association with vascular Dacron grafts and orthopedic joint prostheses: clinicopathologic, immunohistochemical, and molecular study. Ann Diagn Pathol. 2016;21:21–8. DOI: 10.1016/J.ANNDIAGPATH.2016.01.002
14. Lee JB, Jung JW, Kim WO, Ryoo YW, Lee KJ, Kim SA. Case of Rapidly Progressing Angiosarcoma after Total Hip Arthroplasty. Ann Dermatol. 2021;33(4):377–81. DOI: 10.5021/AD.2021.33.4.377
15. Rajan SS, Haider A, Burrell H, Whisker L, Tamimy M, McCulloch T, et al. Angiosarcoma arising in the capsule of a mammary silicone implant. Diagn Cytopathol. 2022;50(5):E119–22. DOI: 10.1002/DC.24919
16. Russo D, Campanino MR, Cepurnaite R, Gencarelli A, de Rosa F, Corvino A, et al. Primary High-Grade Angiosarcoma of the Breast in a Young Woman With Breast Implants: A Rare Case and a Review of Literature. Int J Surg Pathol. 2020;28(8):906–12. DOI: 10.1177/1066896920924087
17. Kakisis JD, Antonopoulos C, Moulakakis K, Taliadoros A, Rontogianni D, Brountzos E, et al. Angiosarcoma of a Thrombosed Arteriovenous Fistula in a Renal Transplant Recipient. Ann Vasc Surg. 2019;56:357.e1-357.e4. DOI: 10.1016/J.AVSG.2018.10.014
18. Brown CJ, Falck VG, MacLean A. Angiosarcoma of the colon and rectum: report of a case and review of the literature. Dis Colon Rectum. 2004;47(12):2202–7. DOI: 10.1007/S10350-004-0698-5
19. Said S, Graham RP, Wu T-T, Yasir S, Zhang L, Folpe AL. Colonic Angiosarcoma Arising in Association with Amyloid Deposits. Case Reports in Gastrointestinal Medicine. 2020;2020:1–6. DOI: 10.1155/2020/3780763
20. Allison KH, Yoder BJ, Bronner MP, Goldblum JR, Rubin BP. Angiosarcoma involving the gastrointestinal tract: a series of primary and metastatic cases. Am J Surg Pathol. 2004;28(3):298–307. DOI: 10.1097/00000478-200403000-00002
21. El Chaar M, McQuay N. Sigmoid colon angiosarcoma with intraperitoneal bleeding and early metastasis. J Surg Educ. 2007;64(1):54–6. DOI: 10.1016/J.CURSUR.2006.09.002
22. Keyser D, Masoumy M, Ham PB, Biddinger P, Rahardja A, Legostaev A, et al. Angiosarcoma of the Colon: https://doi.org/101177/000313481508100412. 2015;111(25):3068–9. DOI: 10.1177/000313481508100412
23. Ma J, Yan Y, He X, Yang Z. Case Report Multiple colonic epithelioid angiosarcoma: a case report and review of literature. International Journal of Clinical and Experimental Medicine. 2018;11(9):10237–43.

24. Fukita Y, Yasuda I, Ishibashi H, Asaki T, Adachi S, Toyomizu M, et al. [Multifocal angiosarcoma of the gastrointestinal tract:a case report]. Nihon Shokakibyo Gakkai Zasshi. 2017;114(9):1665–74. DOI: 10.11405/NISSHOSHI.114.1665
25. Komorowski AL, Darasz Z, Kolodziejski LS, A. G. Primary angiosarcoma of the colon. Acta Chirurgica Belgica. 2004;104(4):465–7. PMID: 15469166

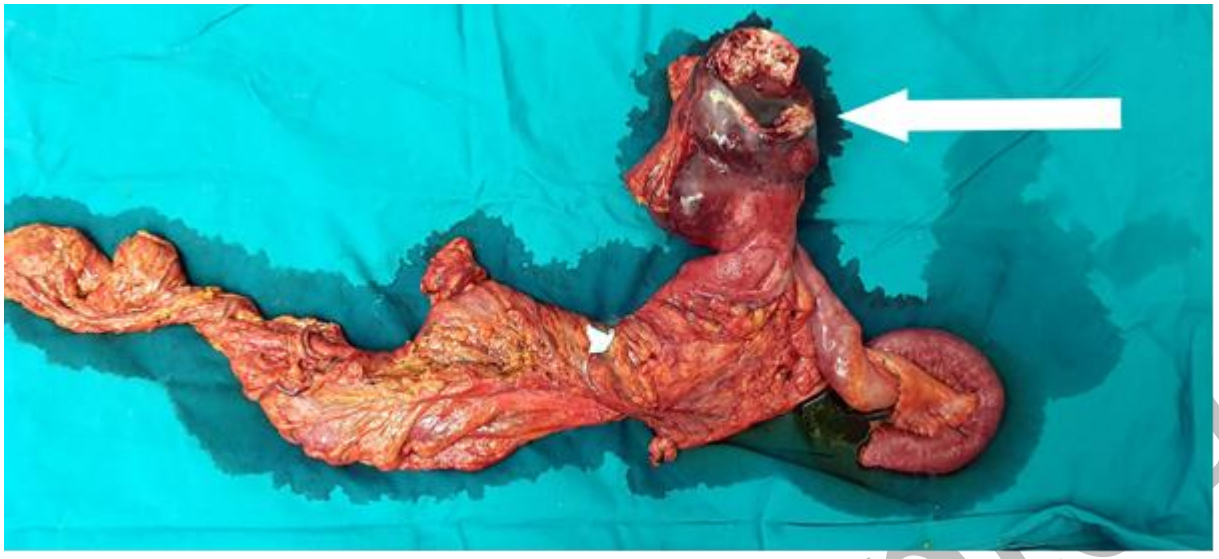

Figure 1. Picture of intraoperative sample; a completely tumor-altered cecum is marked with an arrow

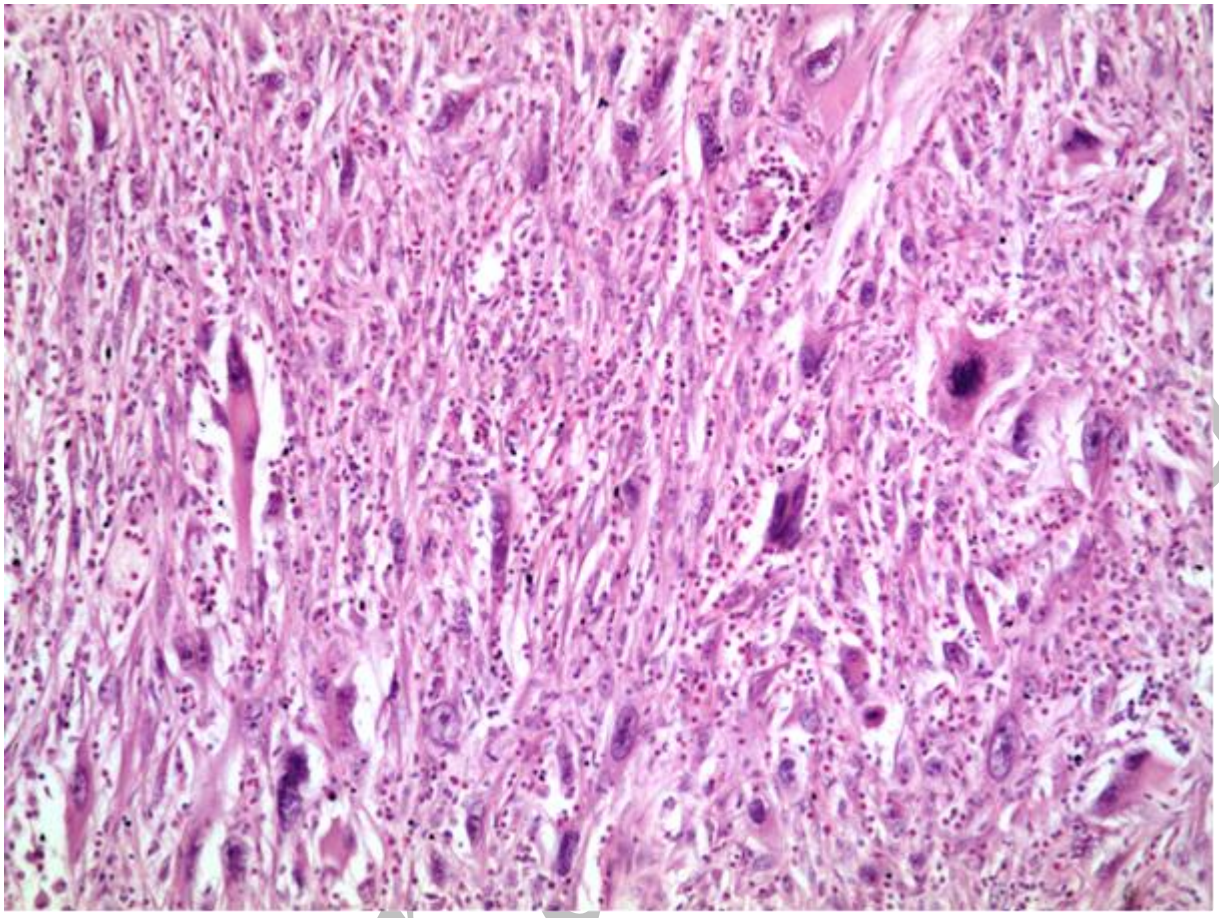

Figure 2. High grade epithelioid angiosarcoma with severe pleomorphism and solid growth pattern; round-polygonal epithelioid cells or spindle cells, with vesicular nuclei containing prominent nucleoli; a few cells were observed to have intracytoplasmic lumina containing erythrocytes or bizarre form (H&E x10)

