Advances in Clinical Medicine 临床医学进展, 2022, 12(1), 694-701
Published Online January 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.121102

Hans汉斯

小肠原发性血管肉瘤一例并文献复习

潘　越，周　璇，赵　涵，赵　鹏*

青岛大学附属医院病理科，山东　青岛

收稿日期：2021年12月26日；录用日期：2022年1月16日；发布日期：2022年1月29日

摘　要

目的：探讨小肠原发性血管肉瘤的组织学特征、免疫组化特征、鉴别诊断和治疗方法。方法：回顾性分析1例小肠原发性血管肉瘤患者的临床资料、组织学诊断及免疫组化结果，并对相关文献进行复习。结果：患者，男，67岁，镜下观察肿瘤由实体性区域和出血坏死区域构成。肿瘤细胞异型性明显，细胞核大呈圆形、多形性，空泡样，具有多形性、间变性特点，核仁大而明显，核分裂象易见，约10个/10HPF；部分细胞胞质丰富，呈嗜双色性。免疫组化显示肿瘤细胞表达CD31、ERG及Fli-1，部分表达CD34。小肠血管肉瘤组织学特征有时可能与其他发生于小肠的肿瘤相混淆，需要与多种肿瘤相鉴别。小肠的血管肉瘤预后较其他部位的血管肉瘤差，本病例患者于术后10个月因全身多脏器转移而死亡。手术切除加术后化疗或姑息性化疗是小肠血管肉瘤的主要治疗方式。结论：小肠原发性血管肉瘤是一种罕见恶性肿瘤，预后差，临床症状无特异性，极易误诊或延迟诊断，因此经常被误诊为其他胃肠道常见病，病理医生需掌握其组织学、免疫组织化学特点及鉴别诊断要点，从而做出准确诊断。

关键词

小肠，血管肉瘤，组织学特征，免疫组化，鉴别诊断

Primary Angiosarcoma of the Small Intestine: A Case Report and Literature Review

Yue Pan, Xuan Zhou, Han Zhao, Peng Zhao*

Department of Pathology, The Affiliated Hospital of Qingdao University, Qingdao Shandong

Received: Dec. 26th, 2021; accepted: Jan. 16th, 2022; published: Jan. 29th, 2022

*通讯作者 Email: qyzhaopeng@sina.com

文章引用: 潘越, 周璇, 赵涵, 赵鹏. 小肠原发性血管肉瘤一例并文献复习[J]. 临床医学进展, 2022, 12(1): 694-701.
DOI: 10.12677/acm.2022.121102

Abstract

Objective: To investigate the histological and immunohistochemical features, differential diagnosis and treatment of primary angiosarcoma of small intestine. Methods: We retrospectively analyzed the clinical data, histological diagnosis and immunohistochemical results of one patient with primary hemangiosarcoma of the small intestine and reviewed relevant literatures. Results: The patient, male, 67 years old. Microscopically, the tumor consisted of solid areas and areas of hemorrhage and necrosis. The tumor cells showed obvious atypia, with large round, pleomorphic and vacuolated nuclei, pleomorphic and anaplastic. The nucleoli were large and obvious, and the mitotic figures were about 10/10HPF. Some cells are rich in cytoplasm, showing dichroism. Immunohistochemistry showed that the tumor cells expressed CD31, ERG and Fli-1, and partially expressed CD34. The histological features of small intestinal angiosarcoma may sometimes be confused with other tumors of the small intestine and need to be differentiated from multiple tumors. The prognosis of angiosarcoma in the small intestine is worse than that in other sites. The patient died 10 months after surgery due to systemic multiple organ metastases. Surgical resection combined with postoperative chemotherapy or palliative chemotherapy has been the main treatment for small intestinal angiosarcoma. Conclusion: Primary angiosarcoma of the small intestine is a rare malignant tumor with poor prognosis and no specific clinical symptoms. It is easy to be misdiagnosed or delayed diagnosis. Therefore, it is often misdiagnosed as other common diseases of the gastrointestinal tract. Pathologists should master the histological and immunohistochemical characteristics and key points of differential diagnosis so as to make a definite diagnosis.

Keywords

Small Intestine, Angiosarcoma, Histological Features, Immunohistochemistry, Differential Diagnosis

1. 前言

血管肉瘤是起源于血管内皮细胞的恶性间叶源性肿瘤，是一种比较少见的软组织肿瘤，约占所有软组织肉瘤的 1%~2% [1] [2] [3]。患者以中老年男性最为常见，好发部位为头颈部的皮肤及软组织，少数病例发生于深部软组织，发生于腹腔脏器的血管肉瘤少见，通常发生于肝脏或脾脏[1]。血管肉瘤恶性程度高，预后较差。本文报道一例发生于小肠的血管肉瘤并复习相关文献总结其临床病理特征，旨在通过对该病例的分析提高对原发性小肠血管肉瘤的认识。

2. 临床资料

患者，男，67 岁，因无明显诱因出现便中带血伴下腹阵发性绞痛及进餐后呕吐而就诊。入院后实验室检查示血常规计数：WBC 10.30 × 10^9/L (参考值：3.5~9.5 × 10^9/L)，血红蛋白 Hb 71 g/L (参考值：115~150 g/L)，血小板 PLT 69.0 × 10^9/L (参考值：125~350 × 10^9/L)；肝功显示白蛋白 ALB 16.10 g/L (参考值：40~55 g/L)，其余实验室检查无特殊；影像学检查 CT 平扫显示左下腹肠套叠(初步定位在空肠区域)。临床初步诊断：肠套叠、消化道出血、中度贫血、低蛋白血症。完善相关检查后，急诊遂行剖腹探查，术中于空

肠近端见约 30 cm 自远向近套叠至 Treitz 韧带，其内可触及质硬肿物；另于小肠内发现三处占位：两处位于空肠、一处位于回肠近端，直径约 2~3 cm，质硬，腔内生长，肉眼侵透浆膜，术中所见考虑恶性肿瘤；遂行小肠肿瘤切除 + 空肠回肠吻合术。

3. 病理学特征

3.1. 大体检查

送检手术切除小肠四段，每段肠管均沿长轴剖开，于肠管内均可见由黏膜向肠腔内生长的隆起带蒂息肉样肿物，共计 8 枚，切片色暗红，质硬，粘膜面部分破溃，直径 1.7 cm~3.3 cm，肉眼侵透浆膜；其余肠粘膜尚光滑，未见特殊。

3.2. 组织学特点

低倍镜下，肿瘤呈息肉样生长，大部分位于粘膜下层与固有肌层内，最深处侵达浆膜。肿瘤由实体性区域(图 1)和出血坏死区域(图 2)构成，实体性区域由大而肥胖的多角形细胞构成，结构分化不明显，少部分区域可见梭形间变性的血管内皮样细胞，部分呈鞋钉样或乳头状或呈血管腔隙样排列，充满大量红细胞(图 3)；肿瘤间质内亦可见大量出血、坏死。高倍镜下，肿瘤细胞异型性明显，细胞核大呈圆形、多形性，空泡样，具有多形性、间变性特点，核仁大而明显，核分裂象易见，约 10 个/10HPF；部分细胞胞质丰富，呈嗜双色性(图 4)。

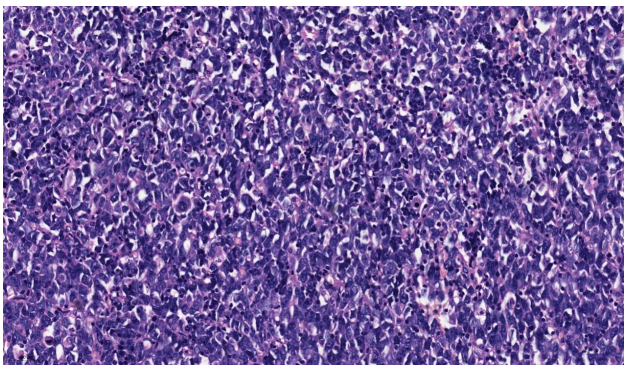

Figure 1. The tumor cells in some areas were solid distribution (HE, ×200)
图 1. 部分区域肿瘤细胞呈实体性分布(HE, ×200)

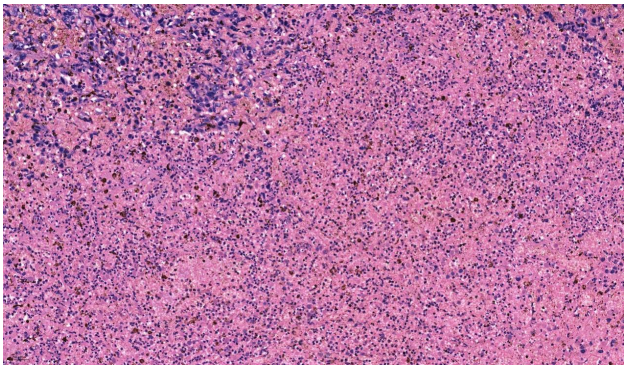

Figure 2. Hemorrhage and necrosis were found in the tumor (HE, ×200)
图 2. 肿瘤内见出血坏死区(HE, ×200)

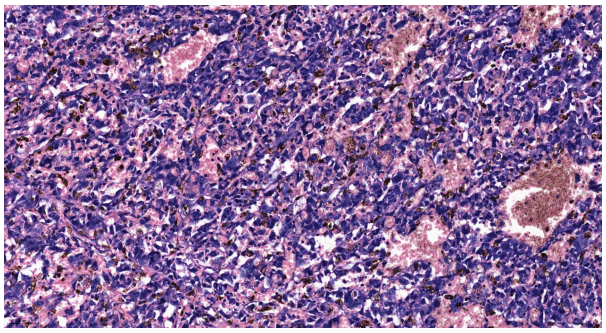

Figure 3. Anaplastic vascular endothelial like cells can be seen in the tumor, some of which are arranged like vascular lacunae and filled with a large number of red blood cells (HE, ×200)
图 3. 肿瘤内可见间变性的血管内皮样细胞，部分呈血管腔隙样排列，充满大量红细胞(HE, ×200)

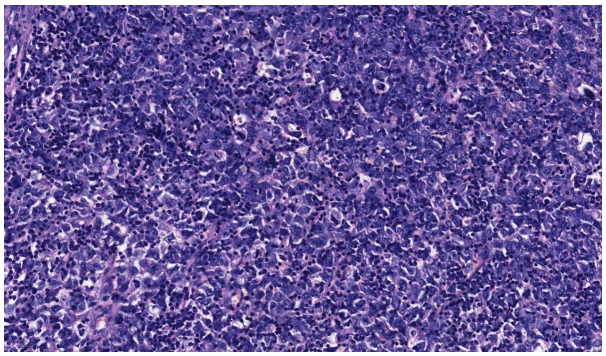

Figure 4. The tumor cells have obvious atypia, large nuclei, round and pleomorphic, vacuolar like, large and obvious nucleoli, easy to see mitotic images, and some cells have rich cytoplasm and are bichromatic (HE, ×200)
图 4. 肿瘤细胞异型性明显，细胞核大呈圆形、多形性，空泡样，核仁大而明显，核分裂象易见，部分细胞胞质丰富，呈嗜双色性(图中可见 5 处病理性核分裂象) (HE, ×200)

3.3. 免疫组织化学

肿瘤细胞 CD31 (+) (图 5)，CD34 部分(+) (图 6)，ERG (+) (图 7)、Fli-1 (+) (图 8)。CK、CD117、Dog-1、S-100、HMB45、Calretinin、WT-1、Syn、CgA、LCA 均(−)，Ki67 指数约 70%。

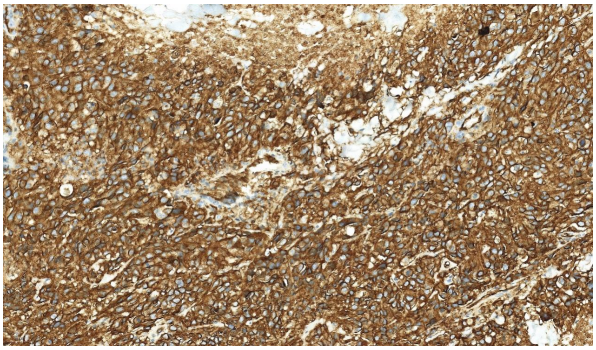

Figure 5. Tumor cells were CD31 positive (HE, ×100)
图 5. 肿瘤细胞 CD31 阳性(HE, ×100)

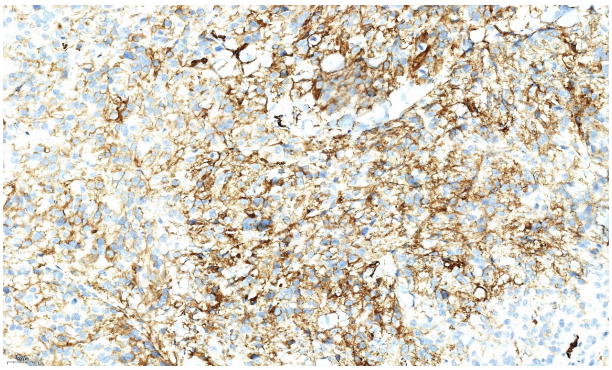

Figure 6. Some tumor cells were CD34 positive (HE, ×100)
图 6. 部分肿瘤细胞 CD34 阳性(HE, ×100)

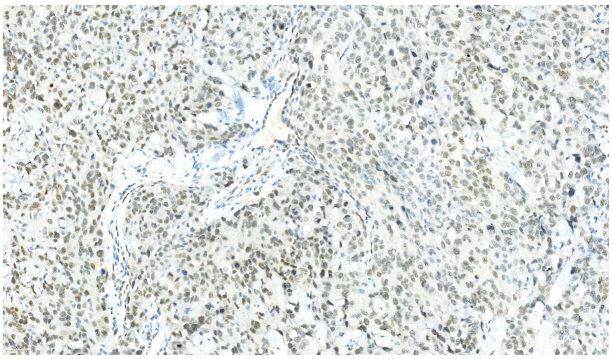

Figure 7. Tumor cells were ERG positive (HE, ×100)
图 7. 肿瘤细胞 ERG 阳性(HE, ×100)

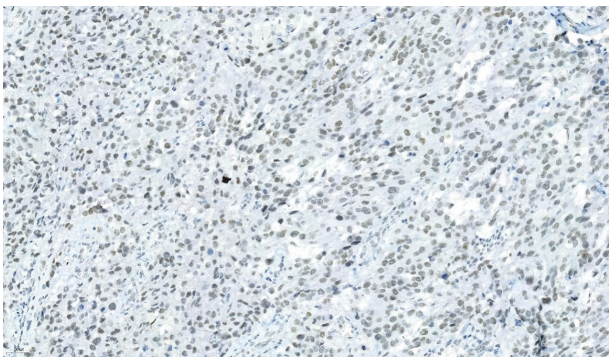

Figure 8. Tumor cell FLI-1 positive (HE, ×100)
图 8. 肿瘤细胞 Fli-1 阳性(HE, ×100)

根据肿瘤镜下形态及免疫组化结果，诊断为小肠原发性多灶性血管肉瘤，肿瘤组织累及肠壁黏膜下层至浆膜层；肠断端未见肿瘤组织。

4. 讨论

原发于小肠的恶性肿瘤是少见的，约占所有胃肠道肿瘤的 2%以下，其中最常见的是腺癌(40%)，其次为神经内分泌肿瘤(25%)、恶性淋巴瘤(10%~15%)和胃肠道间质瘤(9%)等[2] [4]。血管肉瘤是一种少见的软组织恶性肿瘤，仅占所有软组织肉瘤的 1%~2%，肿瘤恶性程度高，预后较差，5 年生存率约为 35% [1] [3]；且血管肉瘤具有较高的侵袭性，常发生远处转移，常见的转移部位有淋巴结、肝脏、肺和骨骼等

[5] [6]。发生于小肠的血管肉瘤则极为罕见，小肠血管肉瘤最常发生的部位是回肠和空肠，国内外文献至今有 67 例报道[7]。

小肠血管肉瘤的临床症状无特异性，包括胃肠道出血、腹痛、恶心呕吐、贫血乏力、肠梗阻等。本病例表现为肠出血，恶心呕吐及肠梗阻而接受急诊手术。由于临床症状无特异性，极易误诊或延迟诊断，因此经常被误诊为其他胃肠道常见病。原发性小肠血管肉瘤的确切病因尚不清楚，但暴露于氯乙烯、放化疗、创伤、长期淋巴水肿等都与其发病有关[8] [9] [10]，该名患者并未表明有相关的临床病史及接触史，确切发病原因尚不能明确。由于血管肉瘤的组织学来源是血管内皮细胞，因此其发生可能与异常的血管生成有关[1]。分子病理学的相关研究表明，在血管肉瘤的发生过程中，血管内皮生长因子(VEGF)及其受体(VEGFr13)的表达相对增加[11]。根据 COSMIC 的数据，人类的血管肉瘤中最常见的基因突变是 KRAS 以及其他 RAS 突变，其中 KRAS 突变占 31%，HRAS 突变占 10%，NRAS 突变占 3% [12]。这些突变基因的发现对于该肿瘤的诊断及对应的靶向治疗具有一定的指导意义。

血管肉瘤以两种生长模式为主，即血管形成和实体性生长，两种生长模式也可以同时出现于同一肿瘤中。本例肿瘤的生长方式即为血管形成与实体性生长模式的混合。血管形成区域的结构可以从形态具有乳头状突出的血管腔隙到裂隙样吻合的血管通道。这些腔隙常常内衬有梭形或肥胖的间变性上皮样肿瘤细胞。上皮样的肿瘤细胞具有丰富的胞浆，常显示中度到明显的核多形性，具有泡状核和大的核仁[13]。免疫组化方面，血管肉瘤常表达血管内皮相关的标志物，CD31、CD34、Fli-1、ERG 能帮助鉴定血管肉瘤，而 CD31 则被认为是血管肉瘤内皮分化最有用的标记物，其他标志物如 VIII 因子、CD34、VEGFR-3 和 ERG 也可能在辅助诊断中发挥一定作用[8] [9] [14] [15] [16] [17]。因此多种标记物的联合应用有助于提高血管肉瘤诊断的敏感性和特异性。

小肠血管肉瘤组织学特征有时可能与其他发生于小肠的肿瘤相混淆，需要与以下肿瘤相鉴别：① 低分化癌：肿瘤的细胞异型性明显、核多形性显著，肿瘤细胞多呈巢团样排列，极少出现血管腔隙样排列，免疫组化表达细胞角蛋白，不表达血管内皮标志物；② 恶性黑色素瘤：该肿瘤的细胞形态多样，可表现为上皮样细胞样，但肿瘤细胞多排列成巢团样，无血管腔隙样结构，免疫组化肿瘤细胞 S-100、HMB-45 及 MelanA 呈阳性表达，血管内皮标志物呈阴性；③ 上皮样胃肠道间质瘤：该肿瘤多发生于胃和小肠，其瘤细胞常呈巢团样或实片样排列，无血管腔隙样结构，胞质可呈嗜酸性，也可呈透亮或呈空泡状，肿瘤细胞常表达 Dog-1、CD117，血管内皮标志物表达为阴性；④ 恶性间皮瘤：根据形态分为上皮样、肉瘤样和双相性三种主要亚型，均可借助肿瘤细胞表达 Calretinin、WT-1、CK5 /6 而内皮标记物阴性进行鉴别；⑤ 上皮样肉瘤：经典型多发生于四肢浅表真皮或皮下，部分病例位于肢体深部软组织；近端型主要发生于盆腔、会阴肛旁区、腹股沟等区域，表现为软组织深部肿块。肿瘤镜下也可呈扩张的血管样，免疫组化 CK 呈阳性，CD31、CD34、ERG 可呈不同程度的阳性，但上皮样肉瘤 INI-1 表达缺失，而血管肉瘤 INI-1 呈阳性；⑥ 间变性大细胞淋巴瘤：肿瘤细胞呈圆形、可见肾形、胚胎形的标志性细胞，细胞弥漫分布，肿瘤细胞表达 CD30、LCA 及 T 细胞标记物，而内皮细胞标记阴性。因此免疫组化染色是鉴别小肠原发性血管肉瘤与其他小肠恶性肿瘤的重要辅助手段。

肿瘤手术切除加术后化疗或者姑息性化疗一直是血管肉瘤的主要治疗方式，且术后辅助化疗的患者比单纯接受手术者预后更好[9]，临床常用的辅助化疗药物有多西紫杉醇，长春瑞滨，舒尼替尼和贝伐珠单抗、帕唑帕尼等[18] [19] [20]。而发生于小肠的血管肉瘤预后较其他部位的血管肉瘤差，大于 1 年生存期的患者极为罕见[7]。

小肠原发性血管肉瘤是一种罕见恶性肿瘤，预后差且经常被误诊为其他胃肠道常见病。掌握其组织学、免疫组织化学特点及鉴别诊断要点并作出明确诊断，将对临床治疗具有重大意义。

声明

该病例报道前已联系病人家属，并在获得其知情同意后报道。

基金项目

国家自然科学基金(81502388)。

参考文献

[1] Young, R., Brown, N., Reed, M., Hughes, D. and Woll, P. (2010) Angiosarcoma. *The Lancet Oncology*, **11**, 983-991. https://doi.org/10.1016/S1470-2045(10)70023-1

[2] 赵志勋, 关旭, 陈瑛罡, 王锡山. 原发性小肠恶性肿瘤诊疗进展[J]. 中华胃肠外科杂志, 2017, 20(1): 117-120.

[3] Shon, W. and Billings, S. (2019) Epithelioid Vascular Tumors: A Review. *Advances in Anatomic Pathology*, **26**, 186-197. https://doi.org/10.1097/PAP.0000000000000228

[4] Reynolds, I., Healy, P. and Mcnamara, D. (2014) Malignant Tumours of the Small Intestine. *Surgeon*, **12**, 263-270. https://doi.org/10.1016/j.surge.2014.02.003

[5] Navarro-Chagoya, D., Figueroa-Ruiz, M., López-Gómez, J., Nava-Leyva, H., Álvarez-Ponce, C., Guzmán-Sombrero, G., *et al*. (2015) Obscure Gastrointestinal Bleeding Due to Multifocal Intestinal Angiosarcoma. *International Journal of Surgery Case Reports*, **10**, 169-172. https://doi.org/10.1016/j.ijscr.2015.03.049

[6] Leong, J., Rascon, M. and Kaushik, N. (2008) Multifocal Angiosarcoma of the Gastrointestinal Tract. E252-E253. https://doi.org/10.1055/s-2008-1077645

[7] Li, R., Ouyang, Z.Y., Xiao, J.B., He, J., Zhou, Y.W., Zhang, G.Y., *et al*. (2017) Clinical Characteristics and Prognostic Factors of Small Intestine Angiosarcoma: A Retrospective Clinical Analysis of 66 Cases. *Cellular Physiology and Biochemistry*, **44**, 817-827. https://doi.org/10.1159/000485345

[8] Takahashi, M., Ohara, M., Kimura, N., Domen, H., Yamabuki, T., Komuro, K., *et al*. (2014) Giant Primary Angiosarcoma of the Small Intestine Showing Severe Sepsis. *World Journal of Gastroenterology*, **20**, 16359-16363. https://doi.org/10.3748/wjg.v20.i43.16359

[9] Nai, Q., Ansari, M., Liu, J., Razjouyan, H., Pak, S., Tian, Y., *et al*. (2018) Primary Small Intestinal Angiosarcoma: Epidemiology, Diagnosis and Treatment. *Journal of Clinical Medicine Research*, **10**, 294-301. https://doi.org/10.14740/jocmr3153w

[10] Squillaci, S., Marasco, A., Pizzi, G., Chiarello, M., Brisinda, G. and Tallarigo, F.J.P. (2020) Primary Post-Radiation Angiosarcoma of the Small Bowel. Report of a Case and Review of the Literature. *Pathologica*, **112**, 93-101. https://doi.org/10.32074/1591-951X-3-20

[11] Young, R., Fernando, M., Hughes, D., Brown, N. and Woll, P. (2014) Angiogenic Growth Factor Expression in Benign and Malignant Vascular Tumours. *Experimental and Molecular Pathology*, **97**, 148-153. https://doi.org/10.1016/j.yexmp.2014.06.010

[12] Bouche, G. andré, N., Banavali, S., Berthold, F., Berruti, A., Bocci, G., *et al*. (2014) Lessons from the Fourth Metronomic and Anti-Angiogenic Therapy Meeting, 24-25 June 2014, Milan. *Ecancermedicalscience*, **8**, 463.

[13] De Francesco, V., Bellesia, A., Corsi, F., Pennella, A., Ridola, L., Zullo, A., *et al*. (2015) Multifocal Gastrointestinal Angiosarcoma: A Challenging Diagnosis? *The Journal of Gastrointestinal and Liver Diseases*, **24**, 519-522. https://doi.org/10.15403/jgld.2014.1121.244.asm

[14] Sullivan, H., Edgar, M., Cohen, C., Kovach, C., HooKim, K. and Reid, M. (2015) The Utility of ERG, CD31 and CD34 in the Cytological Diagnosis of Angiosarcoma: An Analysis of 25 Cases. *Journal of Clinical Pathology*, **68**, 44-50. https://doi.org/10.1136/jclinpath-2014-202629

[15] Huntington, J., Jones, C., Liebner, D., Chen, J. and Pollock, R. (2015) Angiosarcoma: A Rare Malignancy with Protean Clinical Presentations. *Journal of Surgical Oncology*, **111**, 941-950. https://doi.org/10.1002/jso.23918

[16] Wang, Q., *et al*. (2018) Primary Colonic Angiosarcoma Seen in a Patient on Calcium Channel Blocker: A Case Report with Summary Analysis of 32 Other Cases from the Literature. *The American Journal of Case Reports*, **19**, 254-261. https://doi.org/10.12659/AJCR.907287

[17] Xia, J., Shi, D., Wu, Z., Chen, Y., Liu, B., Chen, L., *et al*. (2018) The Poor Prognosis of the Primary Gastric Epithelioid Angiosarcoma: A Case Report. *Medicine* (*Baltimore*), **97**, e0287. https://doi.org/10.1097/MD.0000000000010287

[18] Agulnik, M., Yarber, J., Okuno, S., von Mehren, M., Jovanovic, B., Brockstein, B., *et al*. (2013) An Open-Label, Multicenter, Phase II Study of Bevacizumab for the Treatment of Angiosarcoma and Epithelioid Hemangioendotheliomas.

Annals of Oncology, **24**, 257-263. https://doi.org/10.1093/annonc/mds237

[19] Cuadra-Urteaga, J., Font, A., Tapia, G., Areal, J. and Taron, M. (2016) Carcinosarcoma of the Upper Urinary Tract with an Aggressive Angiosarcoma Component. *Cancer Biology & Therapy*, **17**, 233-236. https://doi.org/10.1080/15384047.2016.1139237

[20] Kollár, A., Jones, R., Stacchiotti, S., Gelderblom, H., Guida, M., Grignani, G., *et al*. (2017) Pazopanib in Advanced Vascular Sarcomas: An EORTC Soft Tissue and Bone Sarcoma Group (STBSG) Retrospective Analysis. *Acta Oncologica*, **56**, 88-92. https://doi.org/10.1080/0284186X.2016.1234068