Composite hemangioendothelioma (CHE) is a rare, locally aggressive, vascular tumor of intermediate-/low-grade malignancy, and is characterized by varying combinations of benign, low-grade malignant, and malignant vascular components. In cutaneous localization, only 22 cases have been reported so far. A new case of CHE of the gluteal region in a 58-year-old man is described. Microscopically, vascular neoplasm, situated mainly within the deep dermis and the subcutaneous fat tissue, was composed of sinusoidal hemangioma, arteriovenous hemangioma, retiform hemangioendothelioma (RHE), and angiosarcoma. An average number of mitoses within the angiosarcomatous component was 10 per 10 high-power fields. Immunohistochemically, the tumor cells were positive for factor VIII-related antigen, CD34, and CD31 and negative for D2-40 and GLUT-1. Ki-67 labeling index was 21%, 1.2%, and 0% in the areas of angiosarcoma, RHE, and sinusoidal hemangioma, respectively. No recurrent disease was noted 3 months after the surgery. The present case displayed the following features previously undescribed in CHE: a novel component of sinusoidal hemangioma and localization at the gluteal region. We also provide review of clinical, histopathological, and immunohistochemical characteristics of cutaneous CHE from the published cases.
case report

Figure 1. Panoramic view of the large part of cutaneous composite hemangioendothelioma (Hematoxylin eosin, original magnification ×12.5).

Figure 2. Retiform hemangioendothelioma composed of long arborizing blood vessels with a hobnail appearance of the lining cells (Hematoxylin eosin, original magnification ×200).

Figure 3. Sinusoidal hemangioma characterized by closely packed, thin-walled interconnecting vascular channels forming a sinusoidal pattern (Hematoxylin eosin, original magnification ×100).

Figure 4. Arteriovenous hemangioma featuring collections of large, thick-walled vessels (right) set near the sinusoidal hemangioma (left) (Hematoxylin eosin, original magnification ×40).

Figure 5. Angiosarcomatous component exhibiting irregular vascular channels with mitotic figures (arrowheads) (Hematoxylin eosin, original magnification ×400).

taneous fat (Figure 4). Angiosarcomatous component showed irregular vascular channels with a complex dissecting and anastomosing growth pattern and frequent intraluminal thrombosis. Several foci of necrosis were present. Endothelial cells exhibited mild-to-moderate nuclear atypia and mitoses: mean 10 per 10 high-power fields (HPFs) with up to 5 mitoses/HPF in the most mitotically active areas (Figure 5).

Endothelial cells within all components of the tumor were immunohistochemically positive for factor
Table 1. Clinical, histopathological, and immunohistochemical characteristics of cutaneous composite hemangioendothelioma from published cases.

| Authors                | Case | Sex/ Age, y | Location          | Pre-operative duration | Size, mm     | Histological components | Mitoses | Necrosis | Immunohistochemistry | Treatment and follow-up |
|------------------------|------|-------------|-------------------|------------------------|--------------|-------------------------|---------|----------|----------------------|-------------------------|
| Nayler et al 2000      | 1    | M/42        | Foot              | 12 y                   | 60×45×40     | SCH, EHE, AS            | SCH: 0  | AS: few  | -                    | NSR after 1 y            |
|                        | 2    | F/27        | Foot              | Since childhood        | 7-20         | SCH, EHE, RHE, AS      | SCH: 0  | RHE: 0   | -                    | NSR after 13 y           |
|                        | 3    | M/21        | Finger            | Several months         | 2 nodules of unstated size | SCH, AVM, RHE | SCH: 0  | RHE: 0   | -                    | NSR after 2 y            |
|                        | 4    | M/44        | Finger            | Several years          | 10           | EHE, RHE, AS           | RHE: 0  | AS: few  | -                    | NA                      |
|                        | 5    | F/31        | Foot              | 2 y                    | 10           | SCH, EHE, RHE, AS     | SCH: 0  | RHE: 0   | -                    | NA                      |
|                        | 6    | F/71        | Foot              | 6 y                    | 30-40        | L, EHE, RHE, AS       | RHE: 0  | AS: few  | -                    | Recurrence within 4 y    |
|                        | 7    | M/35        | Hand              | Several years          | 30           | EHE, RHE, AS          | RHE: 0  | AS: 7/10 | HPF                | Below-elbow amputation: NSR after 7 y |
| Reis-Filho et al, 2002 | 8    | F/23        | Forearm, hand     | Since infancy          | 130×130×70   | SCH, CAH, EHE, RHE, ASL | EHE: 6/mm² | RHE: 3/mm² | ASL: 9/mm²   | NSR after 2 y            |
| Biagioli et al, 2005   | 9    | F/46        | Toe               | 3 y                    | 20×15        | SCH, EHE, RHE         | NA      | N        | NA                  | CO2 laser therapy: first recurrence after 2 y; surgical excision: local recurrence after 18 mo; resection of toes: NSR after 1 y |
| Tronnier et al, 2006   | 10   | F/73        | I: Third toe II: Between first and second toe III: Foot IV: Achilles tendon | Few months | 1.5 y | 10 y | 1.5 y | 10 y | | Tumor I: EHE Tumor II: biopsy not performed Tumor III: EHE Tumor IV: SCH | Excision: local recurrence after 20 mo |
| Case Report | Age | Gender | Location | Duration | Size | Histology | Immunohistochemistry | Treatment | Outcome |
|-------------|-----|--------|----------|----------|------|-----------|---------------------|-----------|---------|
| Chu et al, 2006 | 11 F/18 | Axilla | 2 mo | 60 × 45 × 40 | SCH, CAH, CH, AVM, EHE, RHE, KHE, AS | AS: 3/10 HPF RHE mitotically inactive | + | Greater positivity for CD31 than for FVIII and CD34; VEGF in ASL; negativity for: CK, EMA; Ki-67: 8%-42% in AS, 1%-6% in HE, <1% in HVM | Lymph node metastases (RHE) at diagnosis, bone metastases after 4 mo; chemotherapy and radiotherapy: lung, bones, and liver metastases after 2 y; AWRD |
| Fukunaga et al, 2007 | 12 F/39 | Ankle, foot | Since birth | 300 | SCH, L, EHE, RHE, AS | NA | NA | Cases: 12, 13, 15 positive at least focally for 2 of the following: CD31, CD34, or FVIII; negative for D2-40 | Partial excision: AWRD |
| | 13 F/75 | Thigh | 10 y | 35 | EHE, RHE | NA | NA | | Excision: recurrence after 27 mo |
| | 14 F/37 | Upper arm | Since birth | 40 | CAH, L, AVM, A, EHE, RHE, AS | NA | NA | | AWRD since birth |
| | 15 F/22 | Foot | 3 y | 50 | EHE, RHE | NA | NA | | Partial excision; follow-up NA |
| | 16 M/60 | Leg, foot | Since childhood | NA | SCH, EHE, RHE | NA | NA | | Excision: local recurrence and lymph node metastases (EHE) after few months; lymphadenectomy and chemotherapy; AWRD after 1 y |
| | 17 F/82 | Forearm, hand | 4 mo | 50 × 90 | SCH, CAH, EHE, RHE, ASL | ASL: brisk mitotic activity | NA | Positivity for: CD31, CD34, FVIII; EHE: positive for Prox-1; Ki-67: 50% in EHE | Therapy with interferon; follow-up NA |
| | 18 F/23 | Back | 2 y | 30 | SCH, EHE, RHE, AS | AS: 10/10 HPF | NA | Positivity for: CD31; Negativity for CD34, CK7 and S100 | Excision: NSR after 30 mo |
| | 19 F/48 | Thigh | 2 y | 10-15 | CH, SCH, EH, RHE, KS | None | NA | Positivity for: CD34; Negativity for: S100, desmin and keratin | Multiple local recurrences; multiple excisions; lymph node metastases at 2 y; lymphadenectomy, broad en bloc excision with 100-mm margins, chemotherapy and radiotherapy: NSR after 2 y |
case report

| Case Details | Age | Gender | Location | Duration | Histology | Immunohistochemistry | Outcome | Other Treatments |
|--------------|-----|--------|----------|----------|-----------|----------------------|---------|-----------------|
| Tsai et al, 2011 | 20 | F/23 | Foot | NA | 40 | EHE, RHE | NA | NA | Excision: NSR at 7 mo |
| | 21 | M/8 | Elbow | 18 mo | 16 | SCH, RHE | NA | NA | Excision: NSR at 48 mo |
| Tateishi et al, 2012 | 22 | F/34 | Nose | 7 mo | 8x8 | EHE, RHE | NA | NA | Treatment with electron beam: NSR at 9 mo |
| Present case | 23 | M/58 | Gluteal region | Several years | 27 | SH, AVH, RHE, AS | + | AS, 10/10 HPF; RHE: 0/HPF; SH: 0/HPF | Excision: NSR at 3 mo |

*Note: NSR = No Sign of Recurrence, HPF = High Power Field, AS = Angiosarcoma, AVH = Arteriovenous Hemangioma, AVM = Arteriovenous Malformation, AWD = Alive without disease, AWRd = Alive with residual disease, CAH = Cavernous Hemangioma, ch = Capillary Hemangioma, ehe = Epithelioid Hemangioendothelioma, he = Hemangioendothelioma, hVM = Hemangioma/Vascular Malformation, Khe = Kaposiform Hemangioendothelioma, KS = Kaposi sarcoma, l = Lymphangioma, NA = Not Available, nA = Not available, nSR = No Sign of Recurrence, Rhe = Retiform Hemangioendothelioma, Sch = Spindle cell hemangioma, Sh = Sinusoidal Hemangioma.*

VIII-related antigen (Clone F8/86, Dilution 1:25, Dako, Glostrup, Denmark), CD34 (Clone QBEnd10, 1:25, Dako), and CD31 (Clone JC/70A, 1:20, Dako) and negative for D2-40 (Clone D2-40, 1:200, Dako) and GLUT-1 (Polyclonal, 1:200, Lab Vision, Fremont, CA). Ki-67 (MIB-1, 1:25, Dako) labeling index was 21% in the angiosarcomatous component, 1.2% in the retiform HE, and 0% in the sinusoidal hemangioma.

Histological and immunohistochemical findings were consistent with a diagnosis of CHE. No recurrent disease was noted 3 months after the surgery. The patient was then lost for follow-up.

**DISCUSSION**

CHE is the most recently described vascular neoplasm in the realm of the hemangioendothelioma, included in the 2002 WHO classification of tumors of soft tissue and bone. CHE is defined as a locally aggressive, rarely metastasizing neoplasm with vascular differentiation, containing an admixture of histologically benign, intermediate, and malignant components that merge with each other and vary in their relative proportions.

After the first report of Nayler et al. that included 7 cutaneous CHE cases and 1 in the extracutaneous localization, only 15 additional tumors occurring in the skin/subcutis have been reported so far. The clinical and histopathological features of these cases in addition to our example are shown in Table 1.

The ratio of females to males affected was 2.7:1. The age at presentation ranged from 8 to 75 years (mean, 39 years). In 3 patients, CHEs were present from birth. Previously reported CHEs presented as poorly circumscribed single or multinodular (multicentric) lesions on distal extremities, mostly on hands and feet. Two tumors were situated on the thigh and 1 on the back and in axilla, each. CHE in our patient was localized in the skin of the, previously unreported, gluteal region. In the majority of patients, the preoperative duration of CHEs was long (mean, 16 years; range, 1.5-60 years), and in only 5 patients CHEs developed more rapidly within several months. Individual tumors measured 8 mm to 300 mm in size (mean, 50.6 mm and median 31 mm).

Within the histological components of CHEs, the most frequent were retiform HE and epithelioid HE, occurring in 91%, (20/22) and 86% (19/22) of patients, respectively. The present case was also characterized by the dominant component of retiform HE, occupying approximately 45% of the tumor. Areas similar to angiosarcoma were identified in 54.5% (12/22) of all cases, occupying from less than 1% to 5% when stated. The angiosarcomatous component was more widespread in the CHE reported by Tejera-Vaquero et al and in our case, forming 20%
of the tumor; nevertheless no recurrent tumor was noted after 30 months and 3 months, respectively.

Tumor necrosis was not present in the cases of Nayler et al., and its existence was not mentioned in other CHEs at all except in the gross description of the case of Chu et al.6

Data regarding the mitotic activity in cutaneous CHE are scarce. Mitoses were noted mainly in the angiosarcoma areas, ranging from few mitoses1 to 3 to 10 mitoses/10 HPF1,6,10 similarly to the present case that exhibited 10 mitoses/10 HPF. In the retiform HE component of our case, no mitoses were seen as in the other cases.1,6,11 Exceptionally, Reis-Filho et al recorded 3 mitoses/mm² in the retiform HE, in addition to 6 mitoses/mm² within the epithelioid HE-component.3

Most frequent benign vascular component was the spindle cell hemangioma, found in 14/21 (67%) cases,1,3,12 followed by cavernous hemangioma in 4/21 (19%) cases,3,6,7,9 and arteriovenous malformation and lymphangioma in 3/21 (14%) each.1,6,7 We describe the sinusoidal hemangioma as a benign vascular component of CHE for the first time. Sinusoidal hemangioma is considered to be a variant of cavernous hemangioma,14,15 or an uncommon benign vascular tumor with some similarities to a venous malformation (“cavernous hemangioma”).16

Immunohistochemically, all of the previous cutaneous CHEs expressed 1 or more endothelial markers.1,3,13 Our case was also positive for CD31, CD34, and factor VIII–related antigen but negative for lymphatic endothelial marker D2-40, like the cases of Fukunaga et al.7 Variable immunopositivity for D2-40, observed in retiform HE component,12,13 and positive immunoreactivity for Prox-1 antibody, seen in epithelioid HE component,6 supported a lymphatic line of differentiation in these cases.6,12 HE component6 supported a lymphatic line of differentiation in these cases.6,12 Ki-67 proliferation index has been cited in only 2 reports of CHEs6,6 with up to 42% in angiosarcoma-tous component6 and 50% in the areas of epithelioid hemangioendothelioma.6 In our case, angiosarcoma component exhibited Ki-67 positivity in 21% of cells, while in the areas of retiform HE and sinusoidal hemangioma, Ki-67 index was 1.2% and 0%, respectively, reflecting the differences in proliferative activity of various CHE components.

Regarding the biological behavior of CHE, follow-up data were available in 18 of 22 cases of cutaneous tumors reported previously. Eight patients (44%) were free of the disease,1,3,10,12,13 7 patients (39%) exhibited 1 or more recurrences or residual disease,1,4,5,7,8,11 and 3 patients (17%) developed metastatic lesions in lymph nodes, including 1 patient with additional liver, lung, and bone metastases.8,9,11 Therefore, 55.5% (10/18) of patients with cutaneous CHE had a recurrent and/or metastatic disease. After excisional therapy, local recurrences developed after several months to 4 years.1,4,5,7,8,11 Lymph node metastases were present either at diagnosis,6 or they developed after a few months8 or 2 years.11 Out of 3 CHEs that metastasized, only 1 primary tumor contained a component of angiosarcoma; nevertheless, the lymph node metastases in this case were composed only of RHE.6 Lymph node metastases of the other 2 cases of metastatic CHEs displayed epithelioid hemangioendothelioma1,6 and small-vessel proliferation with many eosinophils.11 These findings confirmed the initial view of Nayler et al that the common presence of an apparently angiosarcomatous component was not associated with a worse prognosis as expected in conventional angiosarcoma.1 CHE should be considered in the differential diagnosis of cutaneous vascular tumors to avoid inappropriately aggressive therapy.

Acknowledgments
This work was supported, in part, by the Serbian Ministry of Education, Science and Technological Development (Project No. 175026).
REFERENCES

1. Nayler SJ, Rubin BP, Calonje E, Chan JK, Fletcher CDM. Composite hemangioendothelioma: a complex, low-grade vascular lesion mimicking angiosarcoma. Am J Surg Pathol 2000;24:352-61.
2. Rubin BP. Composite haemangioendothelioma. In: Fletcher CDM, Unni KK, Mertens F, editors. World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of Soft Tissue and Bone. Lyon: IARC Press; 2002. p. 168-9.
3. Reis-Filho JS, Paiva ME, Lopes JM. Congenital composite hemangioendothelioma: case report and reappraisal of the hemangioendothelioma spectrum. J Cutan Pathol 2002;29:226-31.
4. Biagio M, Buano P, Miracco C, Fimiani M. Composite cutaneous haemangioendothelioma: case report and review of the literature. Clin Exp Dermatol 2005;30:385-7.
5. Tronnier M, Vogelbruch M, Kutzner H. Spindle cell hemangioma and epithelioid hemangiendothelioma arising in an area of lymphedema. Am J Dermatopathol 2006;28:223-7.
6. Chu YC, Choi SJ, Park IS, Kim L, Han JY, Kim JM. Composite hemangioendothelioma. A case report.
7. Fukunaga M, Suzuki K, Saegusa N, Folpe AL. Composite hemangioendothelioma. Report of 5 cases including one with associated Maffucci syndrome. Am J Surg Pathol 2007;31:1567-72.
8. Requena L, Luis Diaz J, Manzarbeitia F, Carillo R, Fernandez-Herrera J, Kutzner H. Cutaneous composite hemangioendothelioma with satellite and lymph node metastases. J Cutan Pathol 2008;35:225-30.
9. Utaa S, Cano O, Ferahbaa A, Ozcan N. Composite cutaneous haemangioendothelioma treated with interferon. J Eur Acad Dermatol Venereol 2008;22:503-5.
10. Tejera-Vaquerizo A, Herrera-Ceballos E, Bosch-Garcia R, Fernandez-Orland A, Matilla A. Composite cutaneous hemangioendothelioma on the back. Am J Dermatopathol 2008;30:262-4.
11. Aydinoglu IE, Demirkasen C, Serdar MA, Mansur AT, Yasar T, Aslan C. Composite haemangiendothelioma with lymph-node metastasis: an unusual presentation at an uncommon site. Clin Exp Dermatol 2009;34:e802-6.
12. Tsai JW, Huang HY, Lee JC, Yen YS, Tung CL, Huang CC, et al. Composite haemangioendothelioma: report of four cases with emphasis on atypical clinical presentation. Pathology 2011;43:176-80.
13. Tateishi J, Saeki H, Ito K, Nakagawa H, Fukunaga M. Cutaneous composite hemangioendothelioma on the nose treated with electron beam. Int J Dermatol 2012;51:e160-2. doi: 10.1111/j.1365-4632.2011.05432.x. [Epub ahead of print].
14. Calonje E, Fletcher CDM. Vascular tumors. In: Fletcher CDM, editor. Diagnostic Histopathology of Tumors. London: Churchill Livingstone, 2007. p. 41-81.
15. Weiss SW, Goldblum JR. Benign tumors and tumor-like lesions of blood vessels. In: Weiss SW, Goldblum JR, editors. Enzinger and Weiss’s Soft Tissue Tumors. St. Louis: Mosby; 2008. p. 633-80.
16. Sangueza OP, Kasper RC, LeBoit P, Calonje E, Lee KC, Chan JK, et al. Vascular tumors. In: LeBoit PE, Burg G, Weedon D, Sarasin A, editors. World Health Organization Classification of Tumors. Pathology and Genetics of Skin Tumors. Lyon: IARC Press; 2006. p. 233-46.