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CASE REPORT

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Chorangioma with trophoblastic proliferation

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Abstract Only two examples of the entity of chorangiocarcinoma, in which there is a proliferation of both the vascular and epithelial components of the placental villi, have been reported in the literature. To test the hypothesis that chorangiocarcinomas are actually more common than implied by the literature, histological sections of chorangiomas were reviewed. Syncytiotrophoblast and cytotrophoblast proliferation, with nuclear atypia, similar to that found in trophoblastic neoplasia, were seen in 15 of 23 cases. Thus, 65% of chorangiomas fulfilled the diagnostic criteria to warrant re-assignment as "chorangiocarcinoma". The proliferation index of the cytotrophoblast in the tumor as measured by MIB-1 (Ki-67) immunostaining was significantly higher in "chorangiocarcinoma" than chorangioma (35.4% vs 15.7%, $P<0.02$). The following factors had no relationship to the presence or absence of trophoblastic proliferation: vascularity, cellularity, infarction, size or location of the chorangioma, or age of the patient. Five of the 15 chorangiomas with trophoblastic proliferation were of the chorangiomatosis variety. No formal follow-up was performed, as this was a retrospective study, but there is no recorded case of persistent gestational trophoblastic disease in this cohort, although one woman with "chorangiocarcinoma" had a history of previous hydatidiform molar pregnancies. An apparently benign clinical course is seen. These lesions, best described as chorangiomas with trophoblastic proliferation, are more common than suggested by the rarity of reported cases.

Key words Trophoblast · Vascular · Proliferation · Chorangioma · Choriocarcinoma

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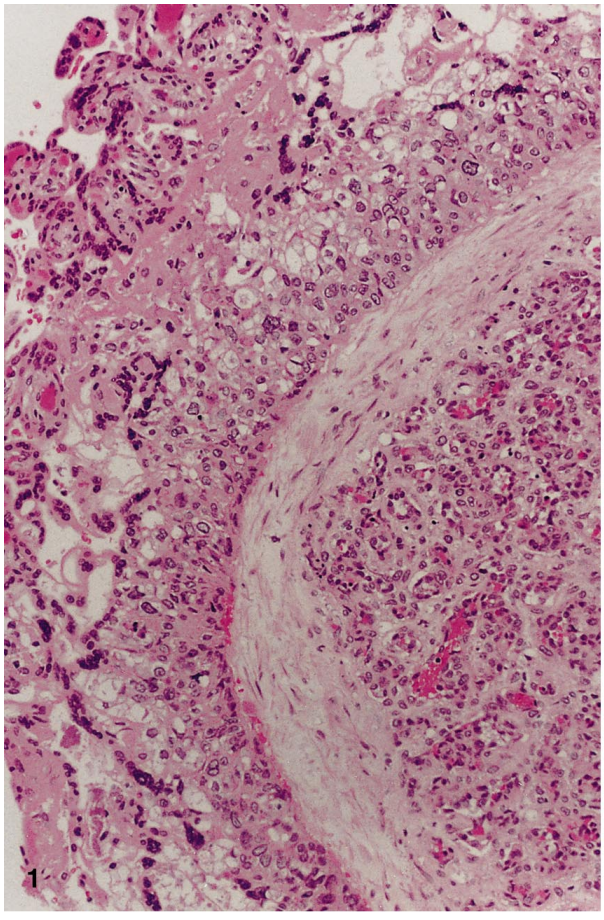
Introduction

Chorangiomas are common lesions, occurring in 1 in 100 placentas, while gestational choriocarcinomas are rare, occurring in 1 in 160,000 normal pregnancies [3]. Jauniaux and his colleagues described a tumor with the typical vascular proliferation of a chorangioma but surrounded by a neoplastic trophoblastic proliferation and proposed the term "chorangiocarcinoma" for the lesion [16]. Since then, only one other case has been described in the literature: a chorangiocarcinoma occurring in one of separate dichorionic diamniotic twin placentas [25]. To test the hypothesis that chorangiocarcinomas are actually more common than implied by the literature, all previous cases of chorangiomas that were diagnosed in the hospital were reviewed.

Material and methods

Cases of chorangiomas between 1982 and 1997 were retrieved from the archival files of the then-Queen Victoria Hospital and Women's and Children's Hospital. Placentas had been triaged according to clinical indications before histological examination. The hematoxylin and eosin-stained sections were reviewed.

Following histological review, immunohistochemistry was performed on representative sections using a streptavidin-biotin peroxidase method with the following antibodies: hPL [diluted 1:1000 in 5% normal goat serum/phosphate-buffered saline (PBS) Dako, Copenhagen, Denmark], hCG (1:10000, Dako), placental alkaline phosphatase (1:100, Zymed, San Francisco, Calif.) and MIB-1 (labeling Ki-67 antigen; 1:100, Zymed). Immunostaining with hCG and MIB-1 was performed following antigen retrieval: dewaxed and rehydrated 5-µm sections were placed in a slide rack and staining dish (Kartell, Lab Supply, Victoria, Australia) containing 0.01 M citrate buffer, pH 6.0, and were microwaved at 650 W until boiling, then for a further 10 min at a 150-W setting in a conventional domestic microwave oven (Sanyo Quickset 650 W); the sections were then allowed to cool and, after a brief wash in PBS, subjected to immunohistochemistry. Sections were incubated with the primary antibodies overnight at room temperature, followed by biotinylated rabbit anti-mouse Ig (1:200, Dako) for placental alkaline phosphatase and for MIB-1, or by biotinylated goat anti-rabbit Ig (1:200, Dako, Denmark) for hCG and for hPL, and, finally, streptavidin-biotin peroxidase (Vector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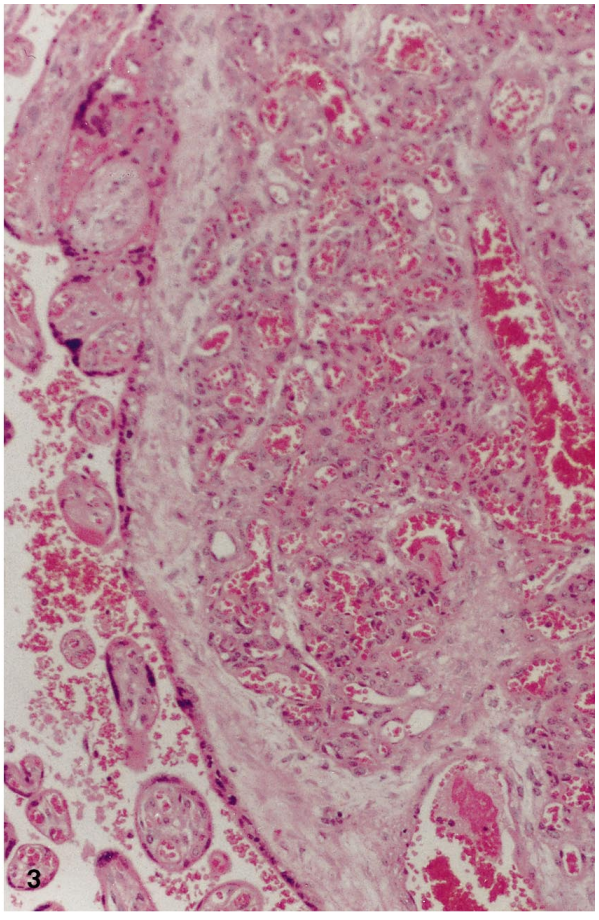
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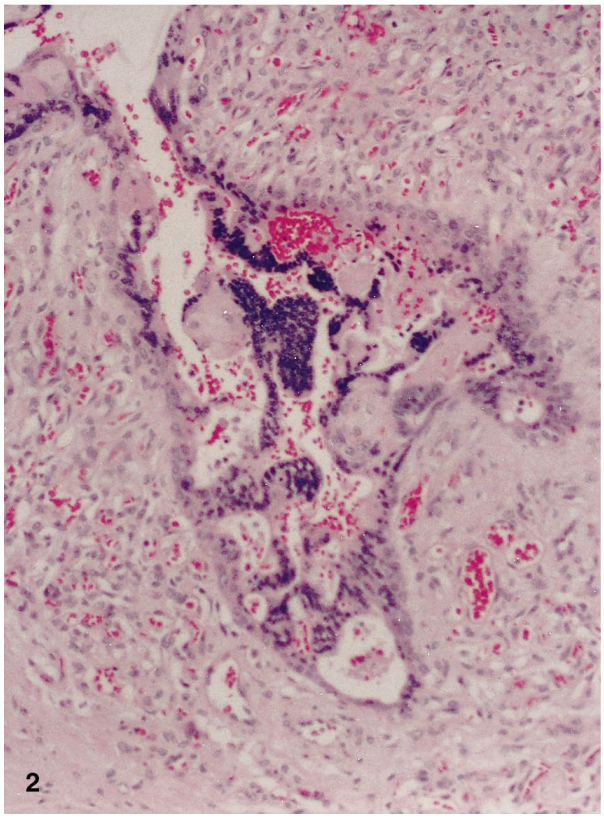
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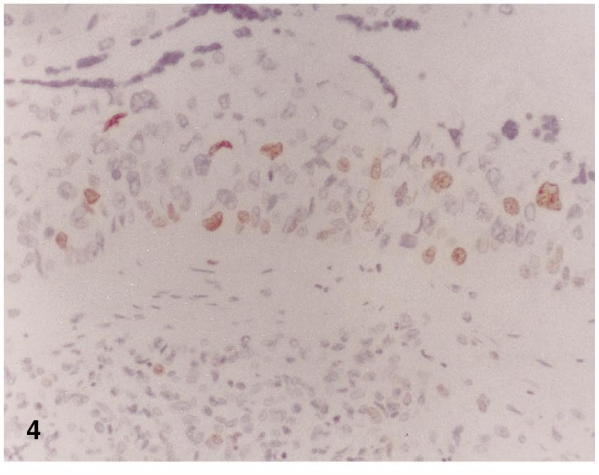
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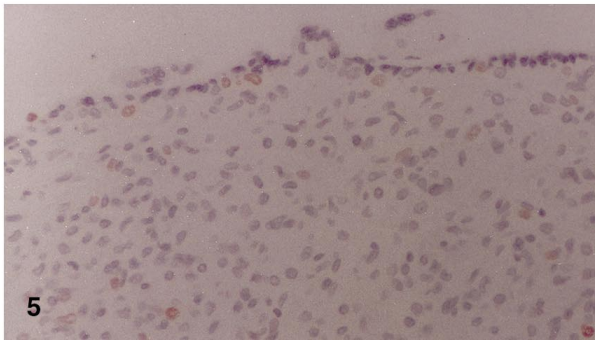
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Elite, Burlingame, Calif.). Immunostaining was developed using 3'3'diaminobenzidene tetrachloride in conjunction with 0.03% hydrogen peroxide, and the sections were lightly counterstained with Mayer's hematoxylin. Tonsillar tissue was used as a positive tissue control for MIB-1, while placental villi acted as internal positive controls for hCG, hPL and placental alkaline phosphatase; negative controls were performed by omitting the primary antibody. A proliferative index was derived by counting the percentage of 100 cytotrophoblastic cells with unequivocal and nuclear MIB-1 staining in the area with the highest staining selected at low power. Comparison between groups was performed with Mann-Whitney U test.

The clinical charts of the women were reviewed. Additional follow-up was undertaken by accessing the Cancer Registry and the Pregnancy Outcome Unit databases of the South Australian Health Commission. Choriocarcinoma but not hydatidiform molar pregnancy is reported to the former, while all forms of pregnancy outcome, including live birth, stillbirth, neonatal death, miscarriage, voluntary terminations of pregnancy and ectopic pregnancy, are reported to the latter.

Results

Twenty six cases of chorangiomas were retrieved from the archival files. The initial diagnoses of chorangioma were confirmed by the typical abundant vascular proliferation supported by villous stroma of variable cellularity. Five of these cases were of the chorangiomatosis variety where there were multiple interconnected nodules of chorangiomas. In 15 cases, syncytiotrophoblast and cytotrophoblast proliferation, with nuclear atypia and pleomorphism, similar to that found in trophoblastic neoplasia, was seen (Fig. 1). Multilayering of cytotrophoblast with fjord-like lacy pattern of the circumference of the trophoblast was seen occasionally (Fig. 2). Seven of the 15 cases with trophoblastic proliferation were associated with a mantle of fibrinoid and degenerate trophoblast. In eight of the 26 cases, there was no proliferation of the investing trophoblastic layer (Fig. 3) while, in three cases, the investing layer of trophoblastic epithelium was lost, and assessment of trophoblastic proliferation was not possible. Thus, 65% of chorangiomas fulfilled the diagnostic criteria to warrant re-assignment as "chorangiocarcinoma".

Immunohistochemistry was not possible in one chorangioma because the tissue had cut out. Strong nuclear MIB-1 staining was seen in the cytotrophoblastic cells in both "chorangiocarcinoma" (average 35.4%, range 10–74%) and chorangioma (15.7%, 10–30%) (Mann-Whitney U test t=2.575, P<0.02). The difference in MIB-1 staining between the two lesions related also to staining in the multiple layers of proliferating trophoblast present in the "chorangiocarcinoma" but in the single layer in chorangiomas (Fig. 4 and Fig. 5). MIB-1 immunopositivity was seen in stromal cells and endothelial cells in five of seven chorangiomas tested and in 7 of 15 "chorangiocarcinomas" (Fig. 5). Normal villi in both "chorangiocarcinomas" and chorangiomas showed positive MIB-1 labeling of cytotrophoblast. In all chorangiomas and "chorangiocarcinomas", the syncytiotrophoblast of the tumors were immunolabeled by hCG, hPL and placental alkaline phosphatase (PLAP), and the intensity was similar to that seen in the normal villi in the rest of the placentas. Cytotrophoblast of the tumors was not labeled by hCG or PLAP but a weaker and focal labeling by hPL was seen.

The following factors had no relationship to the presence or absence of epithelial proliferation: vascularity, cellularity, infarction, size or location of the chorangioma, or age of the patient. All five cases of chorangiomatosis had trophoblastic proliferation.

No formal follow-up was performed, as this was a retrospective study, but review of the clinical charts and the databases of the South Australian Health Commission revealed no antecedent or subsequent reproductive compromise. There is no recorded case of persistent gestational trophoblastic disease in this cohort, although one woman with "chorangiocarcinoma" had a history of previous hydatidiform molar pregnancies. No neonatal or infantile choriocarcinoma is recorded.

Discussion

The presence of choriocarcinomas within placentas is no longer disputed and is described variously as placental choriocarcinoma, intraplacental choriocarcinoma and choriocarcinoma-in-situ [2, 3, 4, 5, 7, 9, 10, 11, 12, 13, 14, 17, 18, 19, 22, 23, 24, 26, 27]. By contrast, only two cases of chorangiocarcinoma, in which placental villous vascular and trophoblastic proliferation are present, have been reported in the literature [16, 25]. Since the cases in this study were identified from placentas that had been triaged for clinical reasons, and chorangiomas are seen in about 1% of pregnancies [3], it is likely that chorangiocarcinoma is more common than suggested by the literature. The defining feature common to these and those previously reported cases is a mantle of atypical trophoblastic proliferation around a chorangiomatous lesion. Although malignant trophoblast protruded into the intervillous space, no avillous malignant trophoblast is seen, and there is no intravillous stromal invasion in chorangiocarcinoma. This may indicate that the term chorangiocarcinoma may be inappropriate and that a descriptive tag of "chorangioma with trophoblastic proliferation" is more applicable to these lesions.

◀ **Fig. 1** Chorangioma with trophoblastic proliferation showing prominent trophoblastic proliferation and villous vascular proliferation (×140)

Fig. 2 Fjord-like lacy pattern of trophoblastic proliferation in a chorangioma with trophoblastic proliferation (×140)

Fig. 3 Typical ordinary chorangioma with vascular proliferation covered by syncytiotrophoblast with occasional underlying cytotrophoblast (×140)

Fig. 4 Immunoperoxidase stain for MIB-1 showing labeling of cytotrophoblast in chorangioma with trophoblastic proliferation. Note also staining of some stromal cells (×280)

Fig. 5 Immunoperoxidase stain for MIB-1 showing labeling of cytotrophoblast and stromal and endothelial cells in chorangioma with trophoblastic proliferation (×250)

Some caution is necessary in interpreting the difference in the proliferative index between the two groups of chorangiomas. The material was archival with no standardization in delivery-to-fixation time interval or fixation time, both of which could affect the proliferation index. The numbers of cytotrophoblasts in chorangiomas in most cases were fewer than in chorangiomas with trophoblastic proliferation, meaning that it was sometimes necessary to assess less proliferative areas to derive the index for the ordinary chorangiomas. Variation in staining of proliferating cytotrophoblasts has been reported in spontaneous abortion, partial and complete hydatidiform moles [6], and suggests a lack of synchrony in the proliferation of cytotrophoblasts within the same placenta. Nevertheless, the difference in the proliferative index, coupled with the morphologic differences of trophoblast atypia and multilayering, point to trophoblastic hyperplasia in the chorangiomas with trophoblastic proliferation.

Follow-up of these patients has been informal, with scrutiny of medical charts and the state health department databases. The period of follow-up, between 15 months and 16 years in this study, would suggest that these chorangiomas with trophoblastic proliferation have a seemingly benign natural history. This would strengthen the argument for not labeling such lesions as chorangiocarcinoma. Although histologically proven cases of intraplacental choriocarcinoma with no metastatic disease in the mother or infant have been described [2, 9, 10, 12, 13], there are, nevertheless, sufficient cases in the literature where histologically proven intraplacental choriocarcinomas have metastasized to mother [4, 5, 7, 8, 11, 14, 17, 18, 19, 21, 22, 23, 24, 26] or to both fetus and mother [1, 27], to at least warrant a close clinical follow-up of women and infants from pregnancies in which a chorangioma with trophoblastic proliferation is found.

The etiology of trophoblastic proliferation in these chorangiomas is perplexing. Both previously reported cases were seen in or surrounded by placental infarct, suggesting that local hypoxia may have led to the trophoblastic proliferation and atypia [20]. In this series, however, trophoblastic proliferation was as likely to be seen in chorangiomas with adjacent fibrinoid and degenerate trophoblast as without. Jauniaux and his colleagues raised the possibility of a chorangiocarcinoma being the "missing link" between lesions showing trophoblastic proliferation and those showing vascular proliferation [16]. It is entirely plausible that growth factors, such as vascular endothelial growth factor and placental growth factor [15, 28], act on both the epithelial and vascular components of the lesion. The interaction of these and other growth factors and their action on trophoblast proliferation and angiogenesis in chorangiomas with trophoblastic proliferation would be worthy of further study.

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References

1. Avril MF, Mathieu A, Kalifa C, Caillou C (1986) Infantile choriocarcinoma with cutaneous tumors. An additional case and review of the literature. J Am Acad Dermatol 14:918–927
2. Barghorn A, Bannwart F, Stallmach T (1998) Incidental choriocarcinoma confined to a near-term placenta. Virchows Arch 433:89–91
3. Benirschke K, Kaufmann P (1995) Pathology of the human placenta, 3rd edn. Springer, Berlin Heidelberg New York, pp 693–716
4. Brewer JI, Gerbie AB (1966) Early development of choriocarcinoma. Am J Obstet Gynecol 94:692–710
5. Brewer JI, Mazur MT (1981) Gestational choriocarcinoma. Its origin in the placenta during seemingly normal pregnancy. Am J Surg Pathol 5:267–277
6. Cheung ANY, Ngan HYS, Chen WZ, Loke SL, Collins RJ (1993) The significance of proliferating cell nuclear antigen in human trophoblastic disease: an immunohistochemical study. Histopathology 22:565–568
7. Christopherson WA, Kanbour A, Szulman AE (1992) Choriocarcinoma in a term placenta with maternal metastases. Gynecol Oncol 46:239–245
8. Douglas GF, Otts OM (1949) Chorionepithelioma associated with normal pregnancy. Am J Obstet Gynecol 57:401–404
9. Driscoll SG (1963) Choriocarcinoma: an "incidental finding" within a term placenta. Obstet Gynecol 21:96–101
10. Duleba AJ, Miller D, Taylor G, Effer S (1992) Expectant management of choriocarcinoma limited to placenta. Gynecol Oncol 44:277–280
11. Flam F (1996) Choriocarcinoma in the term placenta: a difficult diagnosis. Eur J Gynaecol Oncol 17:510–511
12. Fox H, Laurini RN (1988) Intraplacental choriocarcinoma: a report of two cases. J Clin Pathol 41:1085–1088
13. Fukunaga M, Nomura K, Ushigome S (1996) Choriocarcinoma in situ at first trimester. Report of two cases indicating an origin of trophoblast of a stem villus. Virchows Arch 429: 185–188
14. Hallam LA, McLaren KM, El-Jabbour JN, Helm CW, Smart GE (1990) Intraplacental choriocarcinoma: a case report. Placenta 11:247–251
15. Jackson MR, Carney EW, Lye SJ, Ritchie JW (1994) Localization of two angiogenic growth factors (PDECGF and VEGF) in human placentae throughout gestation. Placenta 15:341–353
16. Jauniaux E, Zucker M, Meuris S, Verhest A, Wilkin P, Hustin J (1988) Chorangiocarcinoma: an unusual tumour of the placenta. The missing link? Placenta 9:607–613
17. Kodama S, Yoshiya N, Honma S, Yasuda M, Ikarashi H, Tanaka K (1994) Choriocarcinoma in a term placenta with pulmonary metastasis. Asia-Oceania J Obstet Gynaecol 20:367–373
18. Kudela M, Fingerova H, Tichy M, Talandova A (1984) Choriocarcinoma in pregnancy. Case report. Acta Univ Palacki Olumuc Fac Med 107:367–371
19. Lage JM, Roberts DJ (1993) Choriocarcinoma in a term placenta: pathologic diagnosis of tumor in an asymptomatic patient with metastatic disease. Int J Gynecol Pathol 12:80–85
20. MacLennan AH, Sharp F, Shaw-Dunn J (1972) The ultrastructure of human trophoblast in spontaneous and induced hypoxia using a system of organ culture. A comparison with ultrastructural changes in pre-eclampsia and placental insufficiency. J Obstet Gynaecol Br Commonwealth 79:113–121
21. MacRae DJ (1951) Chorionepithelioma occurring during pregnancy. J Obstet Gynaecol Br Emp 58:373–388
22. Ollendorff DA, Goldberg JM, Abu-Jawdeh GM, Lurain JR (1990) Markedly elevated maternal serum alpha-fetoprotein associated with a normal fetus and choriocarcinoma of the placenta. Obstet Gynecol 76:494–497

23. Santamaria M, Benirschke K, Carpenter PM, Baldwin VJ, Pritchard JA (1987) Transplacental hemorrhage associated with placental neoplasms. Pediatr Pathol 7:601–615
24. Temple-Camp CRE, Ainslie GM (1982) Early gestational choriocarcinoma. A case report. S Afr Med J 62:1040–1041
25. Trask C, Lage JM, Roberts DJ (1994) A second case of "chorangiocarcinoma" presenting in a term asymptomatic twin pregnancy: choriocarcinoma in situ with associated villous vascular proliferation. Int J Gynecol Pathol 13:87–91
26. Tsukamoto N, Kashimura Y, Sano M, Saito T, Kanda S, Taki I (1981) Choriocarcinoma occurring within the normal placenta with breast metastasis. Gynecol Oncol 11:348–363
27. Tsukamoto N, Matsumura M, Matsukuma K, Kamura T, Baba K (1986) Choriocarcinoma in mother and fetus. Gynecol Oncol 24:113–119
28. Vuorela P, Hatva E, Lymboussaki A, Kaipainen A, Joukov V, Persico MG, Alitalo K, Halmesmäki E (1997) Expression of vascular endothelial growth factor and placental growth factor in human placenta. Biol Reprod 56:489–494