CD68 Immunostaining in the Evaluation of Chronic Histiocytic Intervillositis

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• ***Context.*—Chronic histiocytic intervillositis is an uncommon and poorly recognized lesion associated with poor perinatal outcomes, including intrauterine growth retardation and stillbirth. It has a high recurrence rate.**

***Objective.*—To evaluate utility of CD68 immunostaining in the evaluation of chronic histiocytic intervillositis.**

***Design.*—Institutional review board–approved retrospective review was performed. Cases were selected from the departmental archives of University Hospital, Newark, New Jersey, between 2002 and 2009. Controls were from second-trimester pregnancies with chromosomal abnormalities or multiple severe anomalies.**

***Results.*—There were 9 cases and 11 controls. The mean CD68$^+$ count per high-power field for the cases was 88 ± 23 (range, 51–180) and for the controls, 8 ± 5 (range, 0–24), $P < .001$.**

***Conclusions.*—This study establishes a range for histiocyte counts in chronic histiocytic intervillositis and pregnancies without chronic histiocytic intervillositis, and suggests that CD68 staining may have utility in the diagnosis, particularly for nonperinatal pathologists, who may be less familiar with this lesion.**

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Chronic histiocytic intervillositis (CHI) is associated with poor pregnancy outcomes, including intrauterine growth retardation and stillbirth.[1–3] It is thought to be of immune origin, although the exact etiology has not been established. Significantly, there is a risk of recurrence in future pregnancies.[2,3]

Many placentas are signed out by nonplacental pathologists, who may be unfamiliar with CHI as an entity, both in academic centers and in community hospitals. Because of the risk of recurrence, it is important to recognize CHI on placental evaluation, so that clinicians may appropriately follow and develop therapies for these high-risk patients. Chronic histiocytic intervillositis is associated with varying degrees of increased histiocytes in the intervillous space. Normal levels of histiocytes in the intervillous space have not been studied. This study was undertaken to establish a baseline quantification of histiocytes in the intervillous space in pregnancies uninvolved, as well as involved, by CHI and to determine if CD68 immunostaining has clinical utility in the diagnosis.

MATERIALS AND METHODS

Cases of CHI from 2002–2009 were selected from the computer records of the Department of Pathology, University Hospital, Newark, New Jersey, after institutional review board approval. As most of the cases of CHI were from second-trimester complications of pregnancy, and CHI can be seen in all trimesters, controls were selected from second-trimester cases with chromosomal abnormalities or multiple severe anomalies, as cases unlikely to show CHI.

CD68 immunostaining (Dako, Carpenteria, California) was performed by using a standard immunohistochemical protocol.

Slides were evaluated for the number of CD68$^+$ cells in the intervillous space, avoiding areas of abundant red blood cells. Three counts at ×40 (high-power field) were performed, with the pathologist (D.S.H.) blinded as to whether the slide was a case or a control. The means were calculated and the data analyzed by using an unpaired *t* test (Table).

RESULTS

There were 9 cases diagnosed previously as CHI. Eleven controls were evaluated. Minimal clinical history was available for cases, which often came from other hospitals in consultation, but of the 9 cases, 5 were placentas from second-trimester intrauterine fetal demises, 1 of which was also a trisomy 18. A sixth placenta was a subsequent placenta showing recurrent CHI in 1 of the 5 demise cases. No history was available in 3 cases. CD68 immunostaining easily distinguished cases from controls on routine scanning, without the need to perform the actual counts (Figure, A through E). The mean CD68$^+$ count per high-power field for the cases was 88 ± 23 (range, 51–180) and for the controls, 8 ± 5 (range, 0–24), $P < .001$.

COMMENT

Chronic histiocytic intervillositis is an uncommon lesion, and hence may not be recognized by general surgical pathologists. It is associated with poor perinatal outcomes, including growth retardation, recurrent abortions, and stillbirth. Although the etiology is unknown, it is thought to have an immunologic basis, with maternal reaction against placenta a possibility,[1,2] although an

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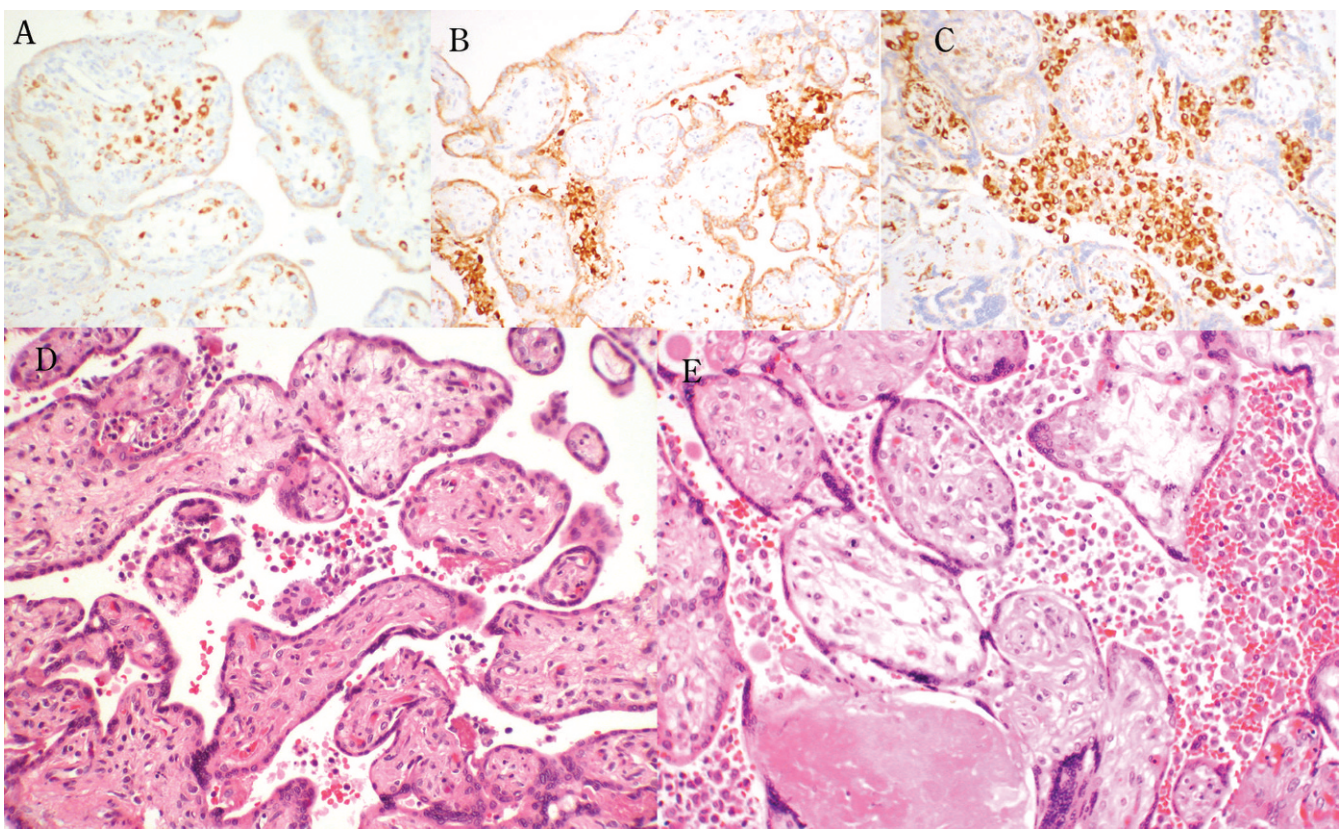
Number of Intervillous CD68+ Cells in Cases of Chronic Histiocytic Intervillositis and Controls					
Case	Count 1	Count 2	Count 3	Mean	SD
1	73	63	91	76	14
2	150	92	124	122	29
3	89	51	71	70	19
4	124	180	71	125	55
5	82	59	52	64	16
6	115	105	77	99	20
7	67	88	45	67	22
8	84	107	74	88	17
9	71	88	83	81	9
Control					
1	0	0	0	0	0
2	11	9	4	8	4
3	16	19	18	18	2
4	0	7	3	3	4
5	10	1	7	6	5
6	8	5	3	5	3
7	7	24	11	14	9
8	15	5	2	7	7
9	0	11	11	7	6
10	5	4	6	5	1
11	10	8	17	12	5

unrecognized infectious process has not been completely eliminated. Rarely, intervillositis may be associated with malaria,[3] but, to our knowledge, in most cases a noninfectious etiology is suspected at this point. Of interest, 2 of the cases described by Traeder et al[4] were associated with assisted reproductive technology, although there is insufficient data to ascribe an association. Chronic histiocytic intervillositis has been suggested to be along the spectrum of the more recognized lesion known as villitis of unknown etiology,[5] along with massive perivillous fibrin deposition and maternal floor infarction.[6] Increased perivillous fibrin is often seen in association with CHI.[7] The incidence of chronic villitis of unknown etiology has been reported to range from 10% to 33% in high-risk pregnancies and from 8% to 14% in the general population.[2] The incidence of CHI is unknown, but probably much lower.[2] Parant et al[2] noted that the difficulty in obtaining an accurate incidence rate relates to the fact that placentas from uncomplicated pregnancies are often not submitted for pathologic evaluation; however, they based the conclusion of rarity of the lesion on finding only 20 cases in a 6-year retrospective analysis and by noting that Boyd and Redline[3] found a similar rate of 6/10,000 in second- and third-trimester placentas evaluated. In the study of Boyd and Redline,[3] the recurrence rate was 67%. Perinatal mortality in this series was 77%, with only 18% of pregnancies reaching 37 weeks. It is important to recognize CHI because it is a potentially recurrent process[2]; therefore, the patient needs to be treated as being at high risk in her next pregnancy. In the series of Parant et al,[2] the recurrence rate was 100%, with more severe histologic findings corresponding to worse clinical outcomes. Although there is no established therapeutic protocol, treatment with corticosteroids and sometimes aspirin has been attempted in some cases.[2,8]



CD68 staining shows no intervillous histiocytes in a control (A) and highlights the cells in 2 cases, one with a lower count (B) and one with a higher count (C). The corresponding hematoxylin-eosin staining is shown in D (lower count) and E (higher count) (original magnifications ×4 [A through C]; original magnifications ×10 [D and E]).

There are no established histologic criteria for the diagnosis of CHI. To our knowledge, no studies performing counts of $CD68^+$ cells in the intervillous space, and correlating the counts to the prior hematoxylin-eosin–based diagnosis, have been published. We found a significant difference between the counts of $CD68^+$ cells in cases and controls. Limitations to the study include the low number of cases, as well as the fact that the prior diagnoses were all made by a placental pathologist, rather than a general surgical pathologist. The choice of controls was based on the autopsy finding of multiple severe anomalies or known genetic abnormality, as the rate of CHI in this group is expected to be extremely low[2] and there was another explanation for the loss. Of interest, one of our cases was subsequently found to have trisomy 18, and it is unclear whether or not the intervillositis is in any way related.

Examination of perinatal specimens, including first-trimester products of conception from pregnancy losses and placentas from complicated pregnancies, is often an area of difficulty for the pathologist who does not specialize in this area. On the basis of consultation cases reviewed, CHI is a poorly recognized lesion in community pathology practice. Histologic evaluation of first-trimester spontaneous abortions is not always undertaken, but CHI may be seen in these specimens as well[9] and may lead to effective treatment of subsequent pregnancies. Diagnosis of the lesion at its first occurrence is difficult. It has been suggested that chorionic villus sampling could be performed to evaluate for CHI at the same time that tissue is obtained for karyotyping in pregnancies with severe growth retardation[10]; however, there are no studies available, and it is not a risk-free procedure. It is important for pathologists to recognize CHI and report it when present. This will allow for the development of treatment protocols that can help with subsequent pregnancies, owing to the high recurrence rate of the lesion. Particularly because the lesion may be focal or show lower but increased levels of histiocytes, CD68 staining may be of assistance in establishing the diagnosis if it is considered. Marchaudon et al[11] have suggested consideration of the diagnosis of CHI in cases of severe pregnancy complications. CD68 staining may be helpful in the evaluation of placentas from poor pregnancy outcomes, for which a specific diagnosis of CHI has not been considered as well, particularly among pathologists who do not specialize in the placenta.

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