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CASE REPORT

Chronic histiocytic intervillositis in consecutive miscarriages: A potential pitfall in routine examination of conceptus

Siti Khadijah MOHD FUAD[1], Nazifah ADZNAN[1], Abd Rahman HAYATI[2], Vikneswaran VIRASAMY[3], Nur Syahrina RAHIM[1,2]*

[1]Department of Pathology and [3]Obstetrics & Gynecology, Hospital Selayang, Ministry of Health, Malaysia. [2]Faculty of Medicine & Health Science, Universiti Sains Islam Malaysia

Abstract

Introduction: Chronic histiocytic intervillositis (CHI) is a rare placental lesion strongly associated with recurrent miscarriages and fetal losses. It requires histopathological diagnosis and can only be made after delivery of the products of conception (POC). We describe a case of CHI in a 41-year-old lady with a 16-year history of thirteen recurrent consecutive first trimester miscarriages. *Case report:* The patient is a 41-year-old lady who suffered first trimester miscarriages in all her thirteen pregnancies. The relevant clinical investigations revealed neither significant nor helpful findings in determining the cause of recurrent miscarriages. Histological findings in each except one of the submitted conceptual tissue showed similar features of histiocytic aggregates primarily within the intervillous spaces, a characteristic description of CHI. One of the samples showed degenerative changes. *Discussion:* Practicing pathologists are not familiar with the histological features of CHI and this may be a potential pitfall in routine examination of POCs. Recognising this entity allows for accurate diagnosis and hence better management. The aetiology remains unclear, although an immunopathological basis are being explored.

Keywords: Recurrent miscarriages, chronic histiocytic intervillositis, massive chronic intervillositis, chronic intervillositis of unknown aetiology.

INTRODUCTION

Chronic histiocytic intervillositis (CHI) is a rare placental lesion with a high rate of recurrence.[1] It is strongly associated with recurrent spontaneous abortions, intrauterine growth restriction (IUGR), fetal loss and demise.[2] The diagnosis requires histopathological assessment of the conceptus and characteristically defined by presence of histiocytic infiltrates predominantly within the intervillous spaces. We describe a case of CHI in a 41-year-old lady who suffered thirteen miscarriages in the last sixteen years.

CASE REPORT

This is a 41-year-old lady who has no living offspring from a total of thirteen pregnancies. They were documented as consecutive first trimester miscarriages in the last sixteen years. The losses occurred between 5 to 12 weeks of gestation. All conceptions were spontaneous and with the same partner of a non-consanguineous marriage. There was no documented history of trauma. Her first presentation was at the age of 25 and had since underwent multiple investigations to determine the cause of her recurrent pregnancy losses. Hysterosalpingogram showed normal uterus and patent fallopian tubes. Serial ultrasound showed no evidence of cervical incompetence. Maternal glucose tolerance test (MGTT) was done as part of the laboratory investigations; the results being 4.8/5.1, 4.5/8.4, 5.0/5.4 and 4.9/4.2 mmol/L. Her thyroid and liver function tests, PT/APTT and serum alkaline phosphatase were within normal range. Thrombophilia screening was negative for both lupus anticoagulant (LA) and anti-prothrombin antibodies (APA). Protein S activity was reported to be slightly reduced. The Protein C level was within normal limit. Other blood investigations such as anticardiolipin antibodies (aCL), antinuclear antibodies (ANA)

**Address for correspondence*: Nur Syahrina Rahim, Faculty of Medicine and Health Science, Universiti Sains Islam Malaysia, Level 13, Persiaran MPAJ, Jalan Pandan Utama, 55100 Pandan Indah, Kuala Lumpur, Malaysia. Tel: +613-3429197. Fax: +603-42982477. Email: *syahrina@usim.edu.my*

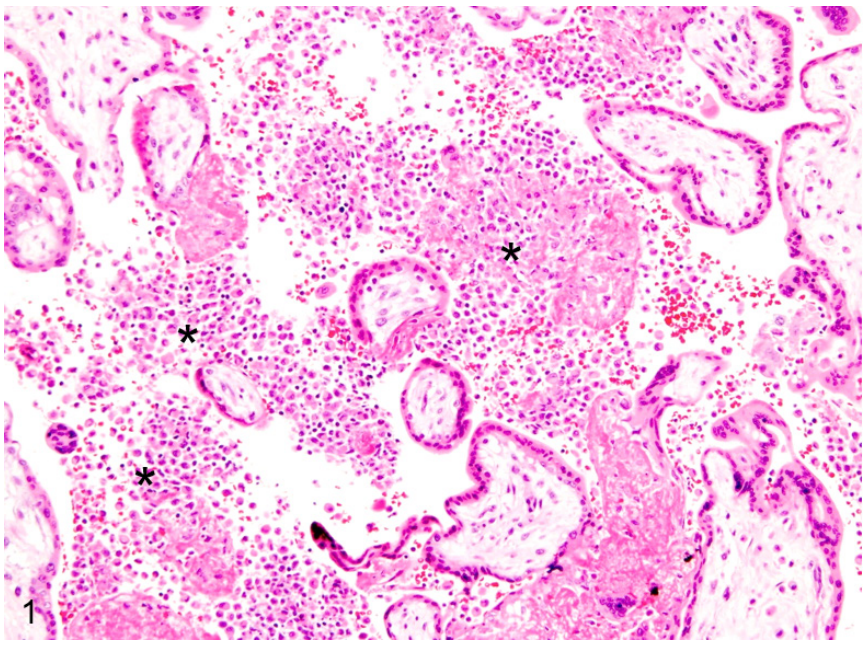

FIG. 1: Diffusely interspersed abundant intervillous aggregates of histiocytes (*) with intervillous fibrin deposition (H&E, x100).

and rheumatoid factor (RF) were all negative. Relevant microbiological investigations did not reveal any significant findings.

The conceptus which was submitted for examination were generally reported as products of conception (POC). However, from each of her other five miscarriages (2nd, 5th, 6th,10th, 13th) no tissue was submitted for histopathological confirmation. In view of the poor obstetric history, the tissue sample from the eleventh conception was referred to and reviewed by our local placental pathologists. There were abnormal aggregates of histiocytes within the intervillous spaces accompanied by fibrin deposition (FIG. 1 and 2). Immunohistochemical staining showed CD 68 positivity, confirming

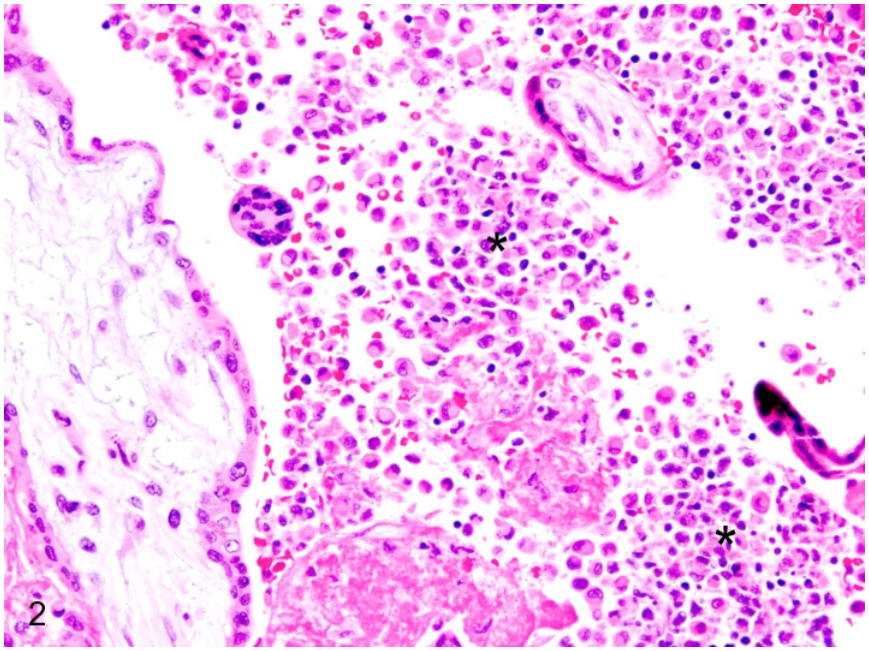

FIG. 2: Higher power view of the intervillous aggregates of histiocytes (*) (H&E, x200).

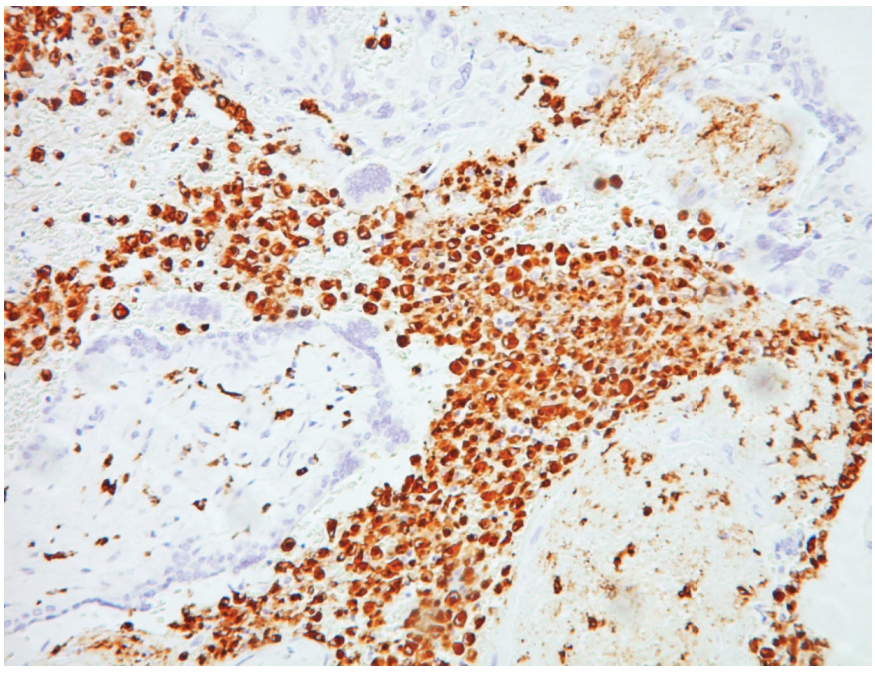

FIG. 3: The histiocytes are CD68 positive (CD68 immunohistochemical stain, x200)

the histiocytic nature of these cells (FIG. 3). No significant villitis were observed. In addition, her previous tissue sections were reviewed and they showed similar histiocytic aggregates. Some tissue showed degenerated changes with intervillous fibrin obscuring these histiocytes (FIG. 4). Based on these findings, a diagnosis of CHI was made. Unfortunately, she presented with her twelfth miscarriage which showed similar aggregates with pronounced extravillous trophoblasts proliferation. Further immunohistochemistry with ICAM-1 showed strong positive reactivity in the histiocytes and focal reactivity in syncytiotrophoblasts (FIG. 5). Her current management plan includes assisted reproduction and initiation of low molecular

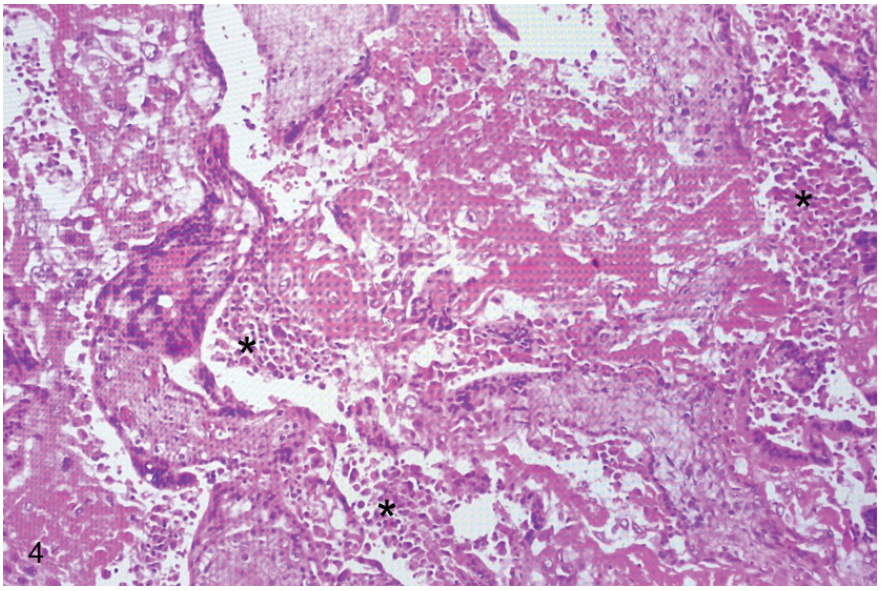

FIG. 4: The histiocytic aggregates (*) within the intervillous space, obscured by intervillous fibrin with degenerated changes (H&E, x100).

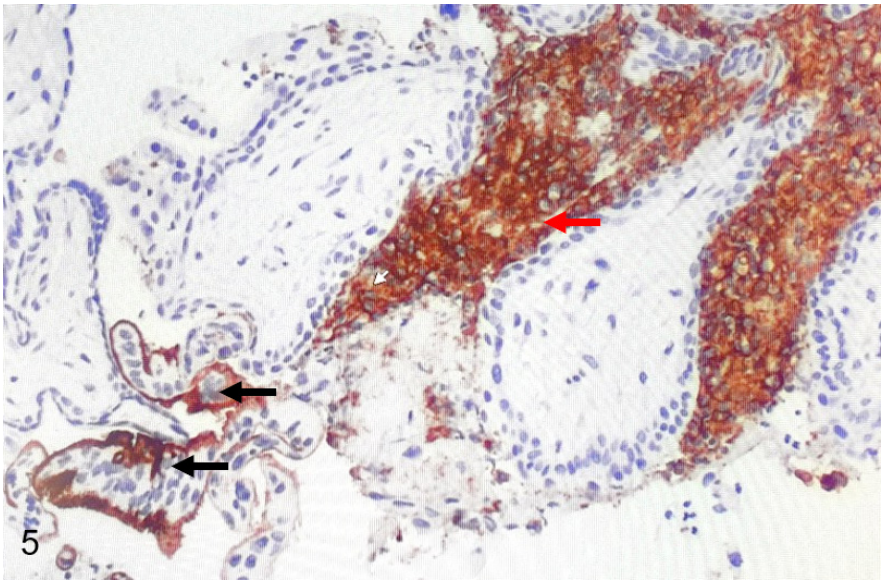

FIG. 5: Immunohistochemical stain with ICAM-1 showed strong reactivity (red arrow) in histiocytes and focal reactivity in syncytiotrophoblasts (black arrow). (ICAM-1 immunohistochemical stain, x200)

weight heparin (LMWH) therapy in the next pregnancy.

DISCUSSION

Labarrere and Mullen had initially described CHI nearly three decades ago as massive chronic intervillositis.[3] Other synonymous terminologies in the literature include chronic intervillositis of unknown aetiology (CIUE) and chronic intervillositis (CI). It is strongly associated with recurrent spontaneous miscarriages, IUGR and fetal demise, despite its rarity and conundrum. The incidence was reported to be higher in first trimester miscarriages (4.4%) compared to second and third trimesters (0.06%) with very high recurrence risk reaching up to 80%.[1,4,5] Up to date and to our knowledge, this case demonstrates the longest history of recurrent consecutive miscarriages before the lesion was appropriately recognised.

The diagnosis requires histopathological examination of products of conception or placental tissue. CHI is characterised by a predominant diffuse histiocytic infiltrate in the maternal intervillous space that may be accompanied by villous or intervillous fibrin deposition.[2,3] These histiocytes may be missed during a routine reporting of tissue from products of conception. This is particularly so if the reporting pathologists are unfamiliar with this entity and/or important clinical information is not being highlighted to the pathologists. Moreover, tissues from recurrent miscarriages are often examined and reported by different pathologists, in a non-specialised tertiary hospital setting. Interestingly, one of the tissue samples showed predominance of implantation site villi in the presence of trophoblastic cell columns which obscured the aggregates of histiocytes. A few other tissues submitted also showed heavy mixture of intervillous fibrin and blood with degenerated villi, shrouding these histiocytes. The CD68 immunohistochemical stain nicely highlights these aggregates, hence proving its usefulness for a general pathologist in supporting their diagnosis.[6]

CHI needs to be distinguished from chronic villitis of unknown aetiology (CVUE). By definition, CVUE too is non-infectious in nature and has a risk of recurrence, particularly in high-grade lesions. It tends to occur in late stages of pregnancy.[7] In contrast to CVUE, the infiltrates in CHI are primarily within the maternal intervillous space. Associated foci of chronic villitis are not uncommonly seen but the infiltrates are rather confined to the villous edge and not villous stroma.[8] A recent systematic review had proposed standardised criteria in defining these intervillous infiltrates.[2] Since the pathogenesis of CVUE also demonstrates an immune origin, both entities can co-exist.[9] CHI are not usually associated with discernable infection, hence cases with clinical or histopathological features of infection should be excluded. Nonetheless, another possible differential diagnosis of chronic

intervillositis is malarial infection.[10] Additional characteristic histopathological findings in malaria include frequent black pigment-laden maternal histiocytes and parasites within the red blood cells.[11] Unlike CHI, chronic intervillositis in malaria has a distinct pathogenesis and no definite risk of recurrence.[1]

Unfortunately, the aetiology of CHI still remains uncertain. The proposed mechanism includes an abnormal maternal immune reaction towards the paternally derived antigens in the conceptus. The flow of maternal histiocytes into the intervillous space causes damage to the syncytiotrophoblasts, crossing this barrier to stimulate an immune rejection response.[12] The ensuing fibrin deposits progressively impair the maternal-fetal exchange. The intervillous infiltrates and syncytiotrophoblasts were shown to have increased ICAM-1 expression.[12,13]

Several maternal factors were found to have some associations with CHI. An underlying autoimmune condition was identified in 29% of cases and occurrence of a number of autoantibodies, including anti-phospholipid.[14-16] There is also a strong association with preeclampsia and maternal vascular malperfusion.[17]

The immunopathological hypothesis has led to the application of immunosuppressive and thrombolytic agents as therapy aimed to prevent recurrence and improve pregnancy outcome, although the efficacy is debatable. Initial review had concluded that there was no benefit in improving the outcome of treated CHI.[1] Nevertheless, a multicenter prospective clinical study had looked into the outcome of pregnancy with different treatment interventions; mono or combined therapy (aspirin, LMWH, prednisone, hydroxychloroquine).[14] The treated cases had shown a significant increment of 35% despite sustained risk of preterm birth at 30% irrespective of treatment regime.[14] Other reports had also shown improved obstetrical outcome.[18,19]

To our knowledge, this case demonstrates the longest history of recurrent first trimester miscarriages associated with CHI. The diagnosis could have been made as early as after the first or third miscarriage, however, the lesion was only recognised in the later episodes. Although the potential treatment may be empirical or not definitely proven, options or other management strategies could have been offered. Nevertheless, relevant clinical histories are crucial and their importance should be emphasised to the reporting pathologist. In situations where there are recurrent poor obstetric outcomes, seeking a second or a subspecialist's opinion would be the best option. Routinely, in doing microscopic examination to confirm products of conception, it is highly recommended that the pathologists keep in mind the possibility of CHI, particularly in the event of repeated miscarriages.

We could confirm the histopathological features of CHI in only seven of the miscarriages, five were not submitted whilst one showed mostly degenerated changes. However, the seven tissue samples with positive findings of CHI represent interspersed samplings of the 13 pregnancy losses throughout the entire period of 16 years. Hence, it could be considered that the recurrent risk of CHI in this lady is 100%.

CONCLUSION

CHI is relatively unfamiliar to practicing pathologists and may become a potential pitfall in routine examination of POCs. Recognising this entity allows accurate diagnosis for subsequent clinical management, particularly in severe cases. The aetiology remains unclear, although an immunopathological basis are being explored. Further studies are required in understanding this entity and in the prevention of recurrent pregnancy losses.

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Authors' contribution: All authors have contributed towards the preparation of final manuscript.

Conflict of interest: The authors declare no conflict of interest.

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