CASE REPORTS

Dendritic cell component in fetal dermatitis

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Abstract

Fetal dermatitis (FD) has been proposed as the cutaneous counterpart of chorioamnionitis. One of its main characteristics is the expression by the inflammatory cells of Toll-like receptors (TLR). Antigen-presenter cells, such as histiocytes, neutrophils and dendritic cells usually express the latter. Histiocytes as well as neutrophils have been demonstrated in the inflammatory infiltrate of FD, but no studies have been performed about dendritic cells. Our objective is to study the population of dendritic cells in cases of FD. We have studied three cases of FD by immunohistochemistry with CD1a antibody. Dendritic cells were present in the dermis as well as in the epidermis of all the cases of FD. Nevertheless, they did not seem to be greater in number from what is considered as normal in a dermis without inflammation. Although our results are not incompatible with a main role of dendritic cells in FD, at least such a role would be plaid without an increase in the number of dendritic cells.

***Keywords*:** fetal dermatitis, toll-like receptor, dendritic cell, CD1a, antigen presenter cell.

Introduction

Fetal dermatitis (FD) was recently proposed as the dermal counterpart of chorioamnionitis induced by bacteria [1].

One of the characteristics of FD is the cutaneous expression of Toll-like receptors, the latter of which plays a crucial role in anti-microbial response. Antigen-presenter cells, such as histiocytes, neutrophils and dendritic cells mainly express these receptors. Some of these cells have already been demonstrated in FD. That is the case for histiocytes or polymorphonuclear cells [1].

Although it is easy to assume that dendritic cells (DC) will also be increased in the skin of fetal dermatitis, no evidence of such a fact has yet been presented. In the present study, we evaluate the presence of dendritic cells by immunohistochemistry in three cases of FD.

Material and methods

Three cases of fetal death human autopsies in which the diagnosis of chorioamnionitis had been morphologically established, were studied in order to demonstrate the presence of dendritic cells in the skin of the foetuses. Skin samples of all the foetuses were studied with routine hematoxylin-eosin stains. In addition, immunohistochemical stains for CD1a were obtained in all the cases (Dakocytomation monoclonal mouse anti-human CD1a, clone 010, code M3571).

Results

Case 1 was a 20-weeks-old intrauterus-death female fetus, of 240 g, without any maternal symptomathology. The examination of the placenta demonstrated intense chorioamnionitis plus funisitis.

The examination of the fetus demonstrated some signs of anoxia. The skin showed mild dermoepidermal, mainly chronic, inflammatory infiltrate, with scattered neutrophils. Some subepidermal bullae were focally found (Figure 1A).

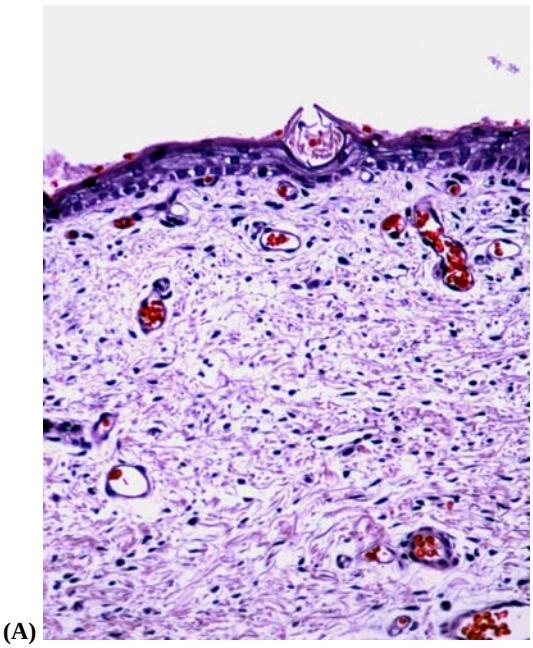
Case 2 was a 24-weeks-old intrauterus-death female fetus, of 568 g, in which spontaneous rupture of the amniotic cavity had been followed by leucorrhoea. A sample from the leucorrhoeic material had been cultured and *Streptococcus beta-agalactiae* had grown from it. The examination of the placenta demonstrated intense acute chorioamnionitis plus funisitis. Changes of *abruptio placentae* were also seen.

The fetus presented signs of acute suffering due to anoxia.

The examination of the skin showed a mild diffuse dermal infiltrate, mainly represented by lymphocytes. Occasional neutrophyls were present; some of them infiltrating the epidermis with occasional micro-abscesses (Figure 1A).

Case 3 was a 16-weeks-old intrauterus-death male fetus, of 119 g, in which also intense chorioamnionitis was demonstrated. The examination of the organs revealed some signs of anoxia. The skin showed only mild inflammatory infiltrate, mainly represented by lymphocytes and histiocytes (Figure 1C).

In these three cases, the immunohistochemical study revealed scattered CD1a positive dendritic cells, mainly among the dermal inflammatory infiltrate, but also occasionally showing intraepidermal location (Figure 2).



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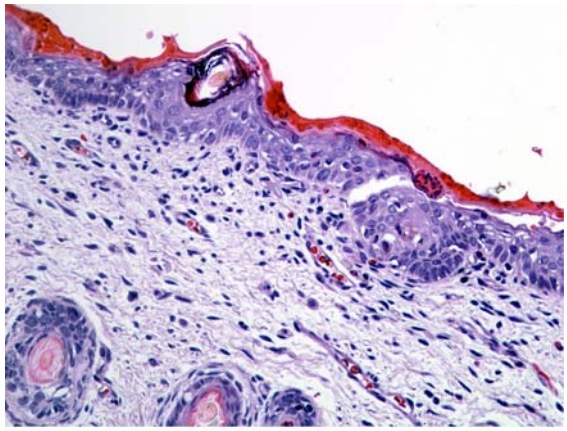

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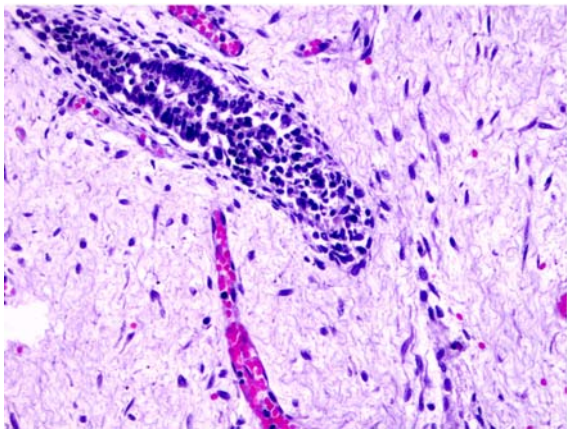
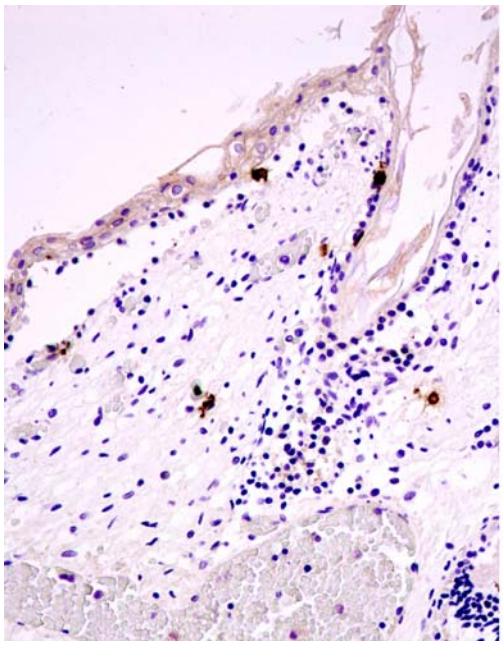


Figure 1 – ***Histopathologic view of the morphological findings in the skin of the three fetuses studied (A – case 1; B – case 2; C – case 3). The inflammatory infiltrate is mild in all three cases, mainly made of chronic inflammatory cells. Case number 1 also shows some neutrophils that occasionally infiltrated the epidermis. Scattered neutrophils were also present in case 2. In case 3 some follicles in formation are shown, with scattered chronic inflammatory cells in adjacent areas***



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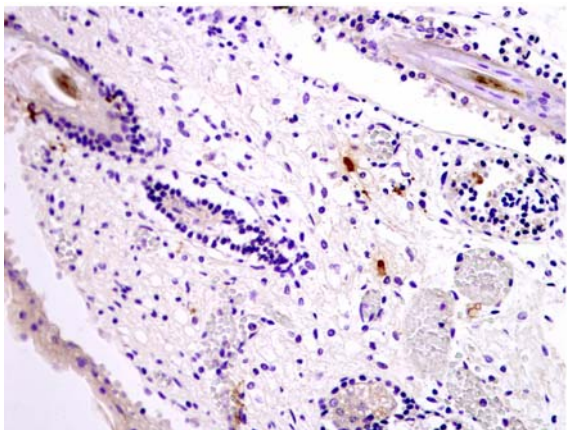

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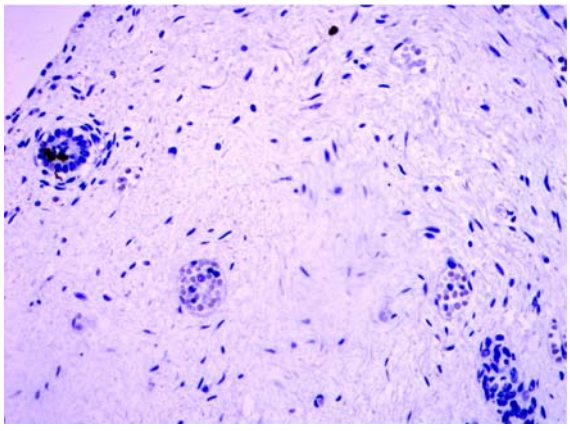

Figure 2 – ***Immunostaining for CD1a (A – case 1; B – case 2; C – case 3). Scattered dendritic cells are present in the dermis, the epidermis and the adnexal epithelium***

Discussions

Fetal dermatitis (FD) has been alleged to be part of the fetal inflammatory response syndrome as the probable fetal counterpart of chorioamnionitis [1].

The morphologic support of FD is mainly made by inflammatory cells like histiocytes, neutrophils and lymphocytes, infiltrating the dermis, as well as the epidermis. Another essential component of this dermatitis is the activation of Toll-like receptors (TLR) [1], which can also be demonstrated in the villous Hofbauer cells of placentas with chorioamnionitis of preterm newborns [2]. These same receptors are expressed in trophoblasts in patients with preeclampsia [3].

TLR are membrane proteins, which recognize structurally conserved molecules from microbes [4], so they play a crucial role in anti-microorganism response. Although it has been demonstrated that TLR response is reduced in premature newborns [5], TLR–2 immuno-reactivity has been proved to be stronger in foetuses with chorioamnionitis than in controls [1].

TLR are mainly located in antigen presenting cells, such as monocytes, macrophages and dendritic cells (DC), but can also be found in granulocytes [6].

Some of these types of cells, as it is mentioned above, have been found in FD, being identified even on immunohistochemical backgrounds. That happens with CD68-positive histiocytes and with CD15 polymorphonuclear cells [1].

Nevertheless, a dendritic cell component had not been investigated in FD yet, to the best of our knowledge, in spite of the crucial role that DC seem to play in the response against bacterial infection [7], and in the subsequent antigen presentation [6].

TLR and dendritic cells are tightly connected in their functions. The fact that TLR activate and mature dendritic cells has been proved through several stimulation ways [7–9].

Dendritic cells, as well as other antigen presenting cells, play a crucial role in the survival of late fetuses, as well as of neonates, against infections [10]. In fact, certain peculiarities of neonatal myeloid dendritic cells, such as decreased upregulation of CD40 and CD80, might be related to the vulnerability of the newborn to infections [11].

We used CD1a as a marker of dendritic cells, and more specifically of cutaneous Langerhans cells. In the latter, CD1a has been demonstrated as essential in the presentation of nonpeptide antigens to T cells [12]. The bacterial glicolipids are loaded into the Birbeck granules of the Langerhans cells, which contain CD1a, before they are presented to T-cells [12]. All these facts prove that Langerhans cells are essential in the immune innate system against infection [12].

Langerhans cells appear in the fetus around the seven week of development but they only start to express CD1a around the 9th week [13].

All our cases were older than that crucial date. Nevertheless, it is considered that it is only after 80–90 days of development when Langerhans cells fully express the CD1a marker. Even though all our cases of fetuses with FD were older than 90 days, the population of Langerhans cells seem to be the same as what it is described in normal dermis: "a few" [13].

Although this finding is not incompatible with the role that they might play in FD, they nevertheless demonstrate that such a role is played without any increase in the number of Langerhans cells.

Conclusions

Our results show no increase in the CD1a cell population in cases of FD. Although this is not incompatible with a main role plaid but these cells in FD, this would happen with no increase in the number of CD1a+ cells.

References

[1] KIM Y. M., ROMERO R., CHAIWORAPONGSA T., ESPINOZA J., MOR G., KIM C. J., *Dermatitis as a component of the fetal inflammatory response syndrome is associated with activation of Toll-like receptors in epidermal keratinocytes*, Histopathology, 2006, 49(5):506–514.

[2] KUMAZAKI K., NAKAYAMA M., YANAGIHARA I., SUEHARA N., WADA Y., *Immunohistochemical distribution of Toll-like receptor 4 in term and preterm human placentas from normal and complicated pregnancy including chorioamnionitis*, Hum Pathol, 2004, 35(1):47–54.

[3] KIM Y. M., ROMERO R., OH S. Y., KIM C. J., KILBURN B. A., ARMANT D. R., NIEN J. K., GOMEZ R., MAZOR M., SAITO S., ABRAHAMS V. M., MOR G., *Toll-like receptor 4: a potential link between "danger signals," the innate immune system, and preeclampsia?*, Am J Obstet Gynecol, 2005, 193(3 Pt 2):921–927.

[4] POLTORAK A., HE X., SMIRNOVA I., LIU M. Y., VAN HUFFEL C., DU X., BIRDWELL D., ALEJOS E., SILVA M., GALANOS C., FREUDENBERG M., RICCIARDI-CASTAGNOLI P., LAYTON B., BEUTLER B., *Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene*, Science, 1998, 282(5396):2085–2088.

[5] FÖSTER-WALDL E., SADEGHI K., TAMANDL D., GERHOLD B., HALLWIRTH U., ROHRMEISTER K., HAYDE M., PRUSA A. R., HERKNER K., BOLTZ-NITULESCU G., POLLAK A., SPITTLER A., *Monocyte toll-like receptor 4 expression and LPS-induced cytokine production increase during gestational aging*, Pediatr Res, 2005, 58(1):121–124.

[6] KHAN S., BIJKER M. S., WETERINGS J. J., TANKE H. J., ADEMA G. J., VAN HALL T., DRIJFHOUT J. W., MELIEF C. J. M., OVERKLEEF H. S., VAN DER MAREL G. A., FILIPPOV D. V., VAN DER BURG S. H., OSSENDORP F., *Distinct uptake mechanisms but similar intracellular processing of two different Toll-like receptor ligand-peptide conjugates in dendritic cells*, J Biol Chem, 2007, 282(29):21145–21159.

[7] CHIEPPA M., RESCIGNO M., HUANG A. Y., GERMAIN R. N., *Dynamic imaging of dendritic cell extension into the small bowel lumen in response to epithelial cell TLR engagement*, J Exp Med, 2006, 203(13):2841–2852.

[8] ZOBYWALSKI A., JAVOROVIC M., FRANKENBERGER B., POHLA H., KREMMER E., BIGALKE I., SCHENDEL D. J., *Generation of clinical grade dendritic cells with capacity to produce biologically active IL-12p70*, J Translat Med, 2007, 5:18.

[9] RAMAKRISHNA V., VASILAKOS J. P., TARIO J. D. JR., BERGER M. A., WALLACE P. K., KELER T., *Toll-like receptor activation enhances cell-mediated immunity induced by an antibody vaccine targeting human dendritic cells*, J Translat Med, 2007, 5:5.

[10] VELILLA P. A., RUGELES M. T., CHOUGNET C. A., *Defective antigen-presenting cell function in human neonates*, Clin Immunol, 2006, 121(3):251–259.

[11] DE WIT D., TONON S., OLISLAGERS V., GORIELY S., BOUTRIAUX M., GOLDMAN M., WILLEMS F., *Impaired responses to toll-like receptor 4 and toll-like receptor 3 ligands in human cord blood*, J Autoimmun, 2003, 21(3):277–281.

[12] HUNGER R. E., SIELING P. A., OCHOA M. T., SUGAYA M., BURDICK A. E., REA T. H., BRENNAN P. J., BELISLE J. T., BLAUVELT A., PORCELLI S. A., MODLIN R. L., *Langerhans cells utilize CD1a and langerin to efficiently present nonpeptide antigens to T cells*, J Clin Invest, 2004, 113(5):701–708.

[13] MURPHY G. F., Histology of the skin. In: ELDER D. E. (ed), *Lever's histopathology of the skin*, Lippincott Williams & Wilkins, Philadelphia, PA, 2005, 9–58.

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