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Ultrastructural demonstration of antigen presenting cells in human uterine tube

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SUMMARY

Langerhans cells (LCs) are the predominant antigen-presenting cells distributed in the mucosa of various organs with high antigenic exposure. They capture antigens, process and present them to the T lymphocytes. LCs are known to be present in the human female reproductive tract. Very few studies have demonstrated the presence of LCs in human uterine tubes. The aim of the present study was to demonstrate the morphology and distribution of LCs in the normal and postpartum human uterine tube by electron microscopy. Tissues from two normal and three postpartum uterine tubes were studied under electron microscopy. The epithelium of the uterine tube varied from simple ciliated columnar epithelium to stratified ciliated columnar epithelium. LCs with a single dendritic process could be identified in the epithelium. The dendritic process displayed the unique Birbeck granules in the cytoplasm. Close apposition of LCs with the intraepithelial lymphocytes was noted. In addition, there were M cells in the epithelium of the normal uterine tube. In the lamina propria, LCs with two or three processes were present which displayed Birbeck granules. They were in close association with lymphocytes as well as with the endothelial cells of the capillaries. A few high endothelial venules (HEVs) were present in the lamina propria of the postpartum uterine tube. The presence of LCs, M cells and HEVs in the uterine tube indicates that the uterine tube is an integral part of mucosa-associated lymphoid tissue.

Key words: Langerhans cell – M cell – HEV – Intraepithelial lymphocyte – MALT

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INTRODUCTION

Dendritic cells are a system of antigen-presenting cells that is distributed in various tissues with high antigenic exposure where they capture antigens, process it and present them to the T lymphocytes. They serve as platforms for initiating T cell responses for both immunity and tolerance (Chung et al., 2007). Langerhans cells (LCs), a subtype of dendritic cells are the predominant antigen presenting cells in the epithelial tissues. They are known to be major histocompatibility complex (MHC) class II expressing bone-marrow derived epidermal dendritic cell (Hamrah et al., 2003).

The female reproductive tract is considered to be part of the mucosa-associated lymphoid tissue (MALT). The local immune system in the female reproductive tract encounters both commensal and pathological microorganisms that multiply in the mucosa (Johansson et al., 1999). The epithelium offers a physical barrier for infection (Iijuma et al., 2008). In addition to this, defense at mucosa surface is mediated through humoral and cell-mediated immunity. Langerhans cells are known to be present in the female reproductive organs including the human vagina (Weiser et al., 2001), the uterine cervix (Figureo and Caorsi, 1980; Morris et al., 1983; Poppe et al., 1996) and the uterus (Hachisuga et al., 1997). Their presence in human uterine tubes has been demonstrated by zinc iodide osmium method (Suganthy et al. 2006). The definite way of identifying Langerhans cell is by showing Birbeck granules by electron microscopy (Rodriguez and Caorsi, 1978; Valladeau et al., 2000). The aim of the present study was to positively identify LCs and other antigen-presenting cells in the uterine mucosa and study their mor-

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phology by electron microscopy.

MATERIALS AND METHODS

Ethical approval was obtained from the Institutional Review Board and informed consent was obtained from all patients who participated in the study. Two normal uterine tube samples were obtained from the ampullary region from patients who underwent abdominal hysterectomy for fibroid uterus, and three postpartum uterine tube samples from patients who underwent puerperal sterilization. Tissues were processed for both light microscopy and electron microscopy. For light microscopy, tissues were fixed in neutral formalin and then processed for immunohistochemistry, embedded in paraffin; 4 µm thick sections were cut. The sections were deparaffinised, antigen retrieval done and stained with polyclonal Rabbit anti-human S100 (dilution 1:100; Dako, CA, USA) and counterstained with Harris haematoxylin. For electron microscopy, tissues were fixed in 3% glutaraldehyde for 3 hours, washed thrice in 0.1M sodium cacodylate buffer at half hourly intervals and post-fixed in 1% osmium tetroxide for 2 hours. After thorough washing in 0.1M sodium cacodylate buffer, the tissue was dehydrated in ascending grades of ethyl alcohol. After dehydration, clearing was done by two 15 minutes changes in propylene oxide and infiltrated with epoxy resin and embedded in the resin mixture. One-micrometer sections were cut using an ultramicrotome (LKB Nova), stained with 1% toluidine blue and viewed under light microscopy. Areas with epithelium were selected for electron microscopy. Ultrathin sections (60-90 nm) were cut from the selected areas on an ultramicrotome (Leica Ultracut UCT, UC7) with a diamond knife (Diatome), and sections mounted on the copper grids. Sections were stained with freshly prepared saturated aqueous uranyl acetate for 1 hour and counterstained with Reynolds lead citrate for 3 minutes. The grids were examined under a Philips EM 201C electron microscope at 40KV.

RESULTS

Immunostaining with S100 showed S100 positive cells in the mucosal layer of the uterine tube (Fig. 1). Ultrastructurally, the epithelium of both the normal and postpartum uterine tube varied from simple ciliated columnar epithelium (Fig. 2a) to stratified ciliated columnar epithelium (Fig. 2b). In the epithelium, different types of cells like ciliated, secretory, peg and undifferentiated cells were noted

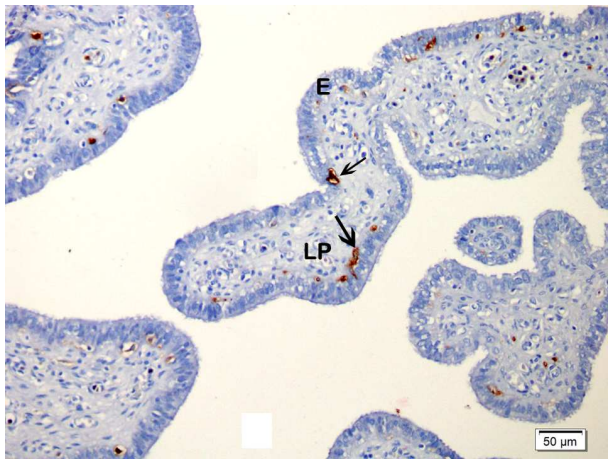
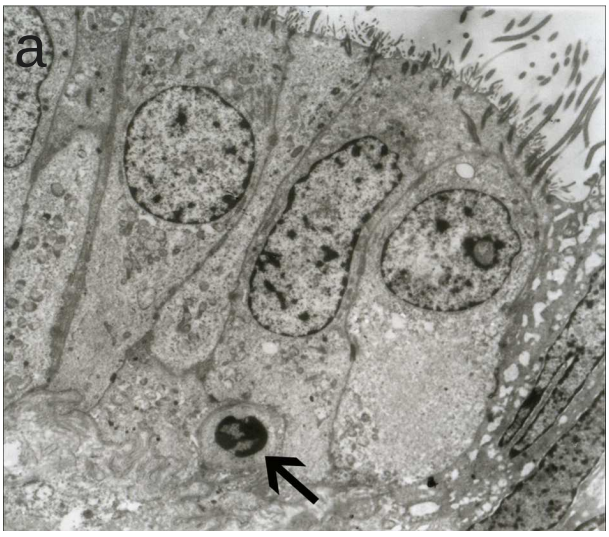


Fig. 1. S100 positive dendritic cells in the mucosa of the uterine tube (arrows). E – epithelium; LP – lamina propria of the uterine tube.



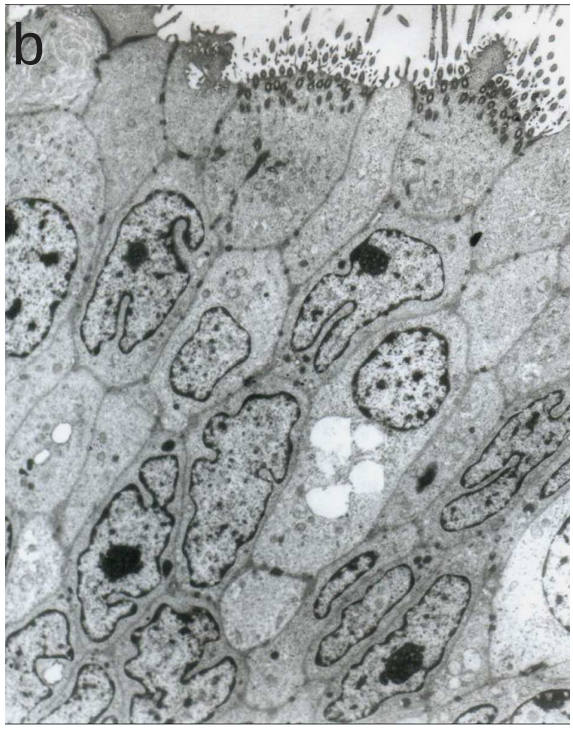


Fig. 2. (a) Electron micrograph of the uterine tube epithelium showing simple ciliated columnar epithelium. Arrow indicates an intraepithelial lymphocyte. x 9428. **(b)** Electron micrograph of the uterine tube showing stratified columnar epithelium. x 10,767.

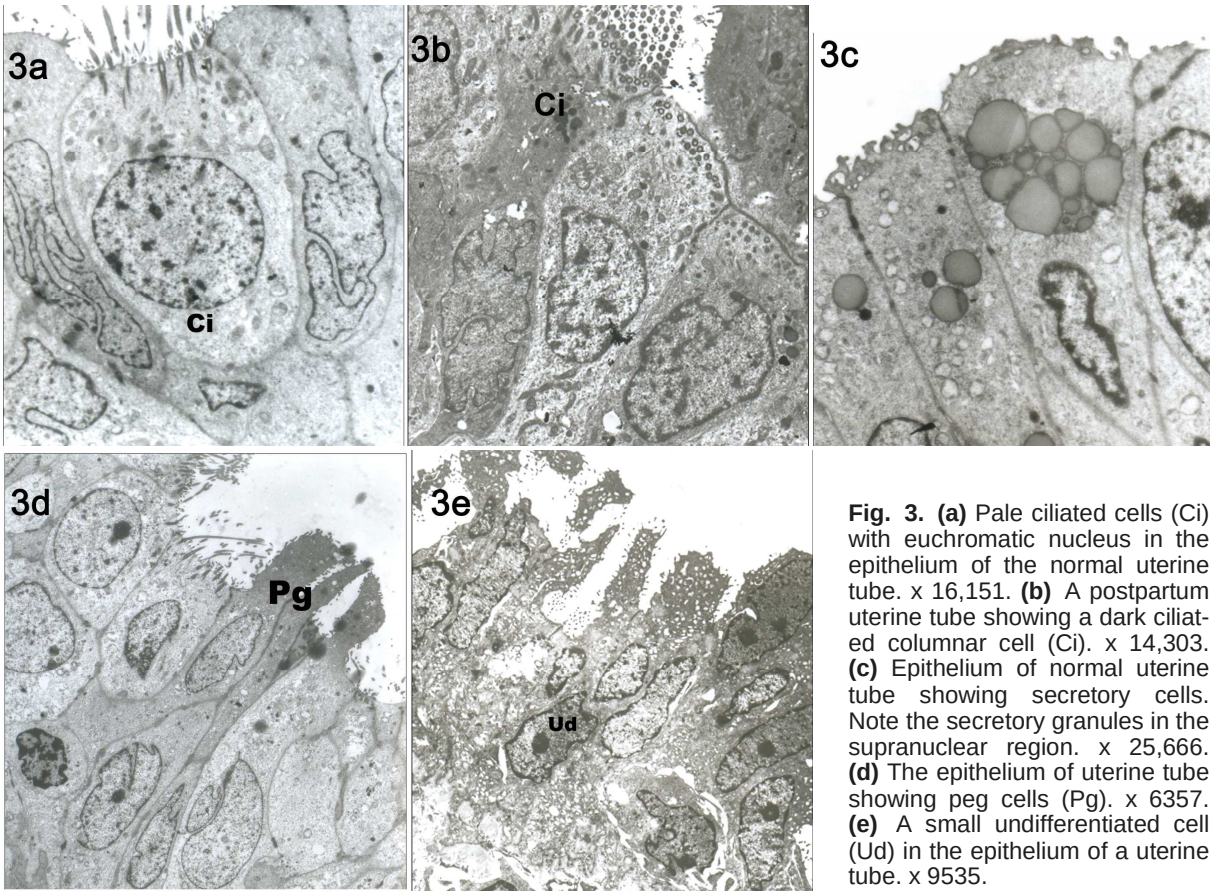


Fig. 3. (a) Pale ciliated cells (Ci) with euchromatic nucleus in the epithelium of the normal uterine tube. x 16,151. **(b)** A postpartum uterine tube showing a dark ciliated columnar cell (Ci). x 14,303. **(c)** Epithelium of normal uterine tube showing secretory cells. Note the secretory granules in the supranuclear region. x 25,666. **(d)** The epithelium of uterine tube showing peg cells (Pg). x 6357. **(e)** A small undifferentiated cell (Ud) in the epithelium of a uterine tube. x 9535.

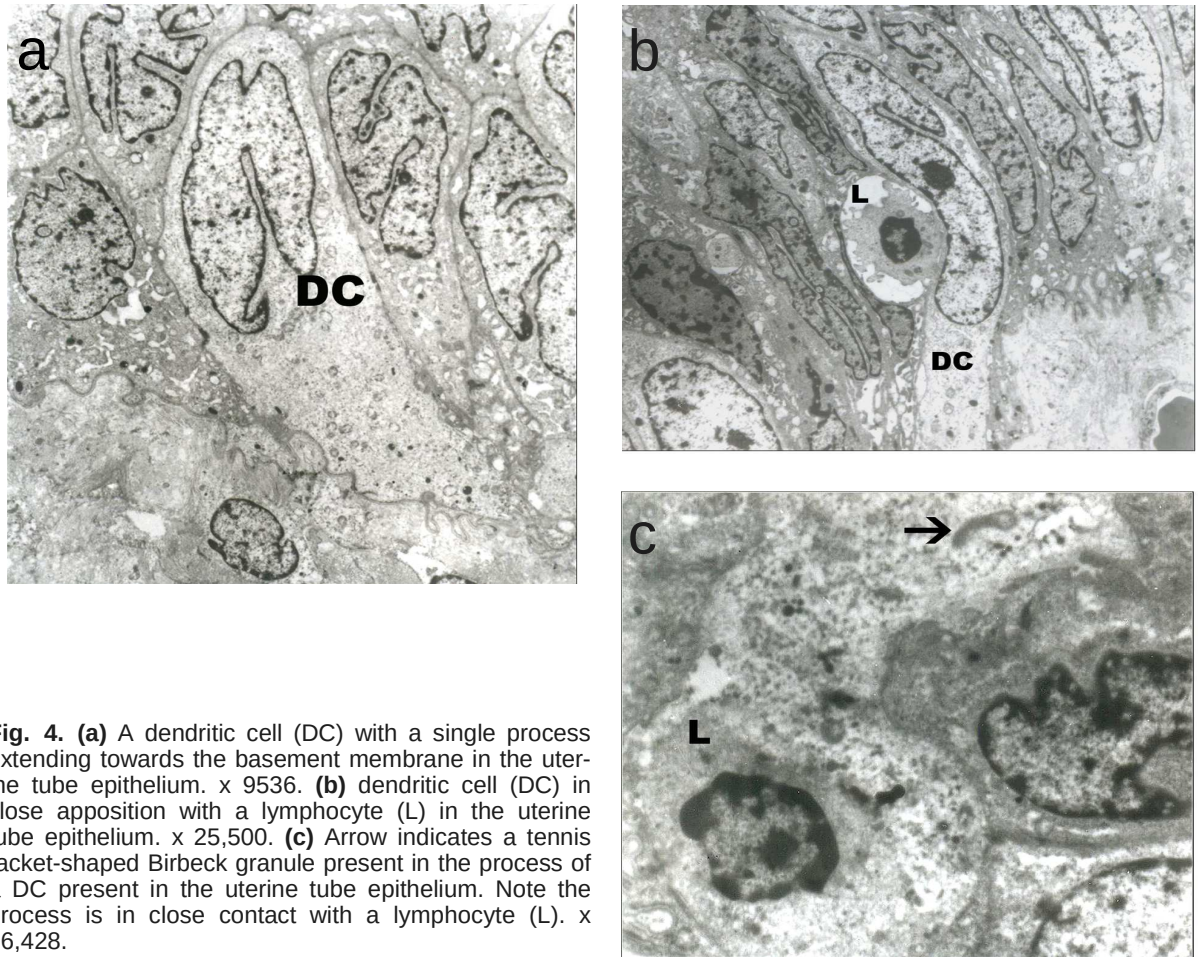


Fig. 4. (a) A dendritic cell (DC) with a single process extending towards the basement membrane in the uterine tube epithelium. x 9536. **(b)** dendritic cell (DC) in close apposition with a lymphocyte (L) in the uterine tube epithelium. x 25,500. **(c)** Arrow indicates a tennis racket-shaped Birbeck granule present in the process of a DC present in the uterine tube epithelium. Note the process is in close contact with a lymphocyte (L). x 36,428.

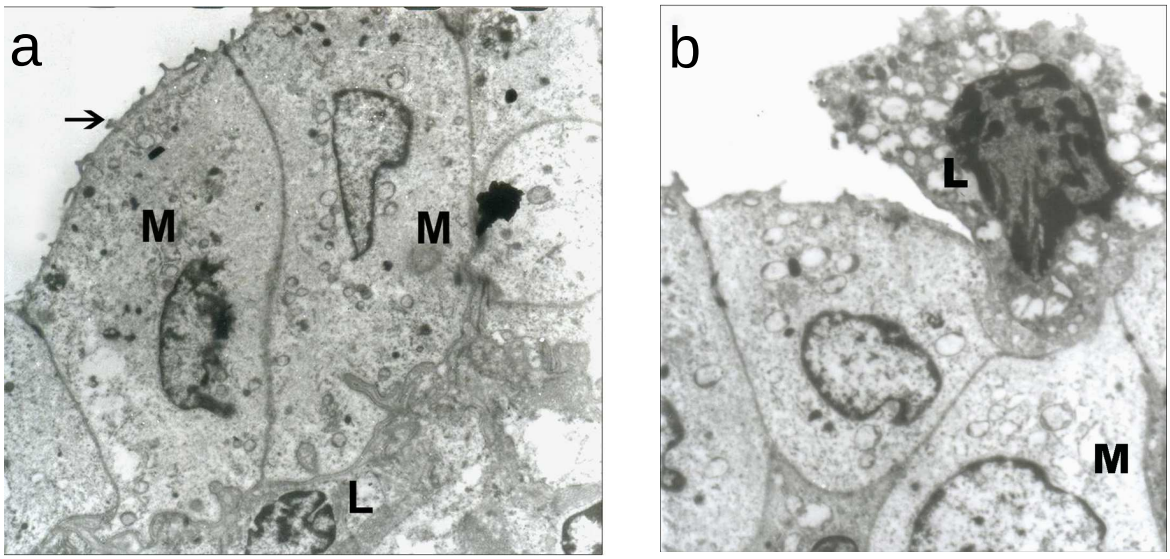


Fig. 5. (a) The epithelium of the uterine tube depicting M cells (M). Arrow indicates the microfolds on the apical surface of the M cell. Note the presence of lymphocyte (L) at the basal surface of M cell. The supranuclear portion has engulfed particles. x 14,303. **(b)** Lymphocyte (L) extruding into the lumen from the apical surface of M cells (M). x 22,250.

(Figs. 3 a-e). In the normal uterine tube, ciliated cells were pale and had round a euchromatic nucleus. Many mitochondria were present in the supranuclear position (Fig. 3a). In the postpartum uterine tube two different types of ciliated cells were noted. In addition to the light ciliated cells with the spherical nucleus, dark tall columnar cells were noted (Fig. 3b). The secretory cells had mucus granules in supranuclear position (Fig. 3c). Among the ciliated and secretory cells, intraepithelial lymphocytes were present (Fig. 2a). Langerhans cells with a single dendritic process directed towards the basement membrane could be identified in the epithelium (Figs. 4a, b). The nucleus was highly indented. The cytoplasm had cell organelles such as lysosomes and mitochondria, but lacked tonofilaments and desmosomes. The dendritic process displayed Birbeck granules in the cytoplasm (Fig. 4c). The close association of the DC with the intraepithelial lymphocyte was noted (Figs. 4b, c). In addition to this, there were M cells in the epithelium of the uterine tube. The M cells had microfolds on the apical surface and engulfed particles on the supranuclear portion. The basal part of the M cells were in close association with the intraepithelial lymphocyte (Fig. 5a). A lymphocyte was extruding into the lumen from the apical surface of the M cell (Fig. 5b).

Langerhans cells were present in the subepithelium too. They had 2 or 3 processes. Figure 6a shows a dendritic cell with two processes in close apposition with a lymphocyte. Rod-shaped Birbeck granules could be identified in the cytoplasm (Fig. 6b). A few dendritic cells in the lamina propria did

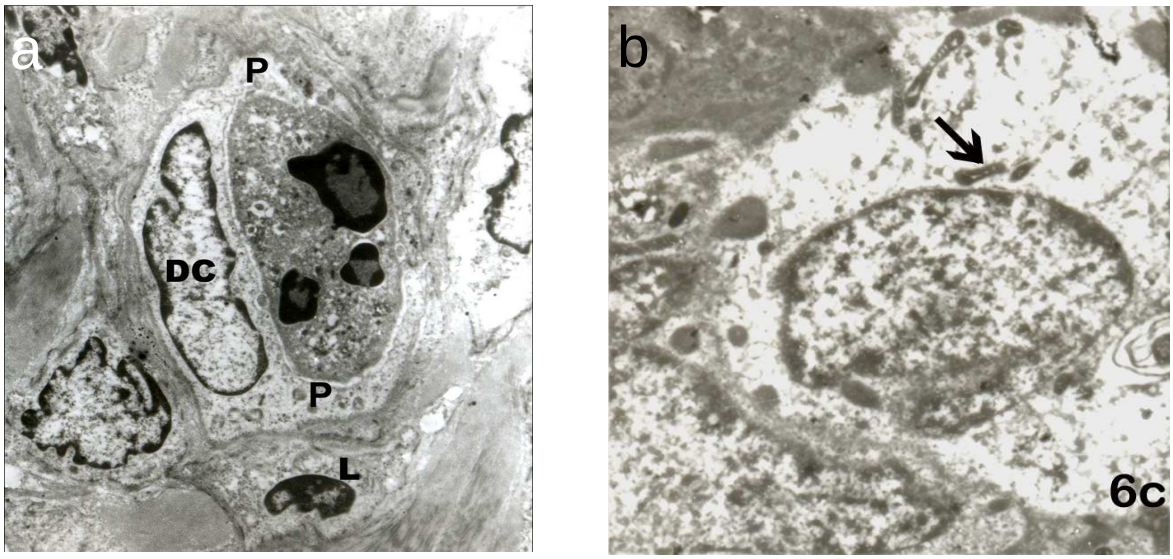


Fig. 6. (a) Dendritic cell (DC) in the lamina propria of the uterine tube with two processes (P) in close apposition with an underlying lymphocyte (L). x 13,875. **(b)** Arrow indicates a rod-shaped Birbeck granule in another LC. x 62,666.

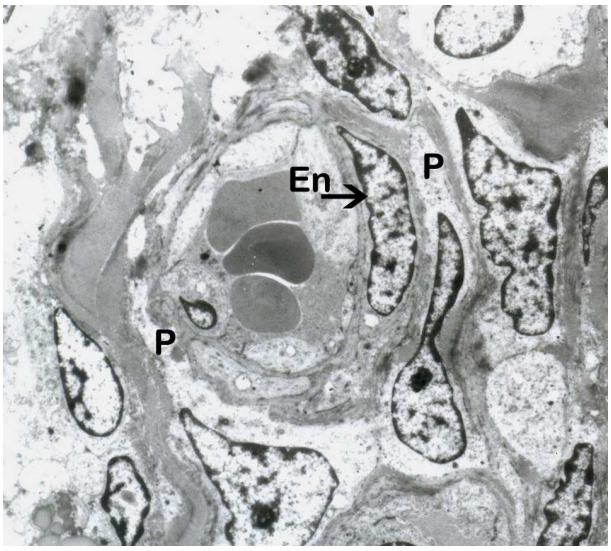


Fig. 7. Arrow indicates an endothelial cell (En) lining the capillary. Note the LCs in close association with the capillary. P – dendritic processes of the LCs. x 9709.

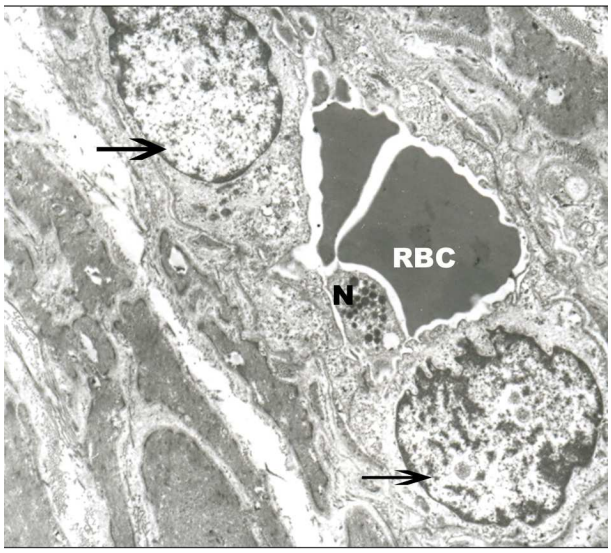


Fig. 8. A high endothelial venule in the lamina propria of a postpartum uterine tube. Arrows indicate the cuboidal endothelial cells. RBC – red blood corpuscle; N – neutrophil. x 16,392.

not have Birbeck granules. The lamina propria of the postpartum uterine tube had lot of blood vessels. Dendritic cells were seen in apposition with the endothelial cells of the capillaries (Fig. 7). High endothelial venules lined by cuboidal endothelium were present in the lamina propria (Fig. 8).

DISCUSSION

The immune system of the female reproductive system is under the influence of ovarian hormones oestradiol and progesterone, which prepare the reproductive tract for successful fertilization, implantation and pregnancy, while the epithelial cells of the female reproductive tract confer protection against potential pathogens by secreting bactericidal agents that inhibit the growth of microorganisms (Wira and Fahey, 2004). The epithelial lining of the uterine tube is composed of at least four types of cells: the ciliated columnar, secretory, peg and undifferentiated cells. Their ratio varies with hormone levels and position. Ciliated cells are much reduced after the menopause. Secretory cells are interspersed among ciliated cells. Peg cells are narrow columnar elements with oval nuclei. They are thought to represent secretory cells in the non-secretory phase of their cycle. Undifferentiated cells are small cells restricted to the epithelial base. They are probably mainly stem cells for the ciliated and secretory cell populations (Williams et al., 1995).

Langerhans cells in uterine mucosa

Langerhans cells (LCs) are immature dendritic cells playing a sentinel role through their specialized function in antigen capture, and their capacity to migrate to secondary lymphoid tissue to initiate specific immunity (Valladeau et al., 2003). Very few studies have demonstrated the presence of LCs in the uterine tube (Hagiwara et al., 1996; Suganthy et al., 2006). In the present study, LCs were identified both in the epithelium and lamina propria of the uterine tube both by light microscopy and electron microscopy. It has been described that markers including CD1a (Krenácse et al., 1993), Langerin (Lau et al., 2008), S100, ATPase, MHC Class II (Tay et al., 1987) and ZIO (Niebauer et al., 1969) have been used to demonstrate the different subpopulations of LCs. S100 protein was first isolated from the bovine brain and later identified in glial and Schwann cells of the nervous system, epidermal LCs and in other cells like myoepithelial cells of the salivary and mammary glands (Turusov, 1990). Most of the S100-positive cells of the lymphoreticular system are dendritic cells involved in the immune response and they belong to the mononuclear/phagocytic system. Although there is lack of specificity with S100 protein, it has been used as an immunohistological diagnostic marker for the malignacicies of the immune system, as it is specifically related to dendritic cell microenvironment (Carbone et al., 1986). S100 protein has been used to identify LCs in the vulva (Taube, 2007) and in uterine endometrium (Coppola, 1998). In the present study, the presence of LCs in the uterine tube mucosa was confirmed by staining the sections with S100. S100 positive cells were identified both in the epithelium and subepithelium. Ultrastructurally, LCs were identified by the presence of intended nucleus and lack of tonofilaments in the cytoplasm and desmosomes. In the epithelium, the cells had a single process, which is directed towards the basement membrane. This is in accordance with the previous study of dendritic cells in uterine the tube using Zinc Iodide Osmium technique (Suganthy et al.,

2006). The dendritic processes displayed the unique Birbeck granules. They are composed of Langerin and are part of endosomal recycling pathway (Romani et al., 2012). Although the Birbeck granules are thought to be important in antigen processing (Stossel et al., 1990), their functions are poorly understood. Birbeck granules could allow internalization of antigens and possibly their storage to delay presentation to T-lymphocytes (Valladeau et al., 2003).

In the subepithelium, LCs had two or more processes and they too displayed the Birbeck granules. Close association of LCs and blood vessels was demonstrated. It has been suggested that the DCs may not be able to pass the endothelium of blood vessels, but with their long processes they form the right microenvironment to retain T cells and B cells during the process of antigen presentation (Kraal et al., 1989).

M cells in the uterine tube

M cells are exclusively present in the dome areas that associated with the submucosal lymphoid follicles. Usually they are present in the small and large intestines. But they have been identified in other lymphoid organs like the palatine tonsils (Indrasingh et al., 1999) and adenoids (Claeys et al., 1996). The interactions of antigens with the apical surface of M cells play an important role in the initial step of intestinal and systemic immune responses or tolerance (Gebert et al., 1996). In the present study, M cells were identified electron microscopically in the uterine tube. The apical surface was characterized by microfolds. The presence of engulfed particles in the M cells confirmed their role in endocytotic uptake at the apical membrane, transcytotic transport and exocytotic release of luminal substances to the intercellular space of the epithelium. M cells were seen in relation to the intraepithelial lymphocytes at the base or in basolateral position. There is evidence that M cells express MHC class II molecules and are capable of presenting antigens to lymphoid cells (Allan et al., 1993). Therefore it can be concluded that M cells are not only involved in the passive antigen transport, but also process and present antigens to the adjacent intraepithelial lymphocytes. In the present study, the surface of M cell ruptured and lymphocytes were liberated into the lumen of uterine tube. The bursting of M cells was previously reported in inflamed mucosa and it was suggested that it could be either due to the hyperplasia of the underlying lymphoid tissue which resulted in stretching of the M cell or due to increase in endosomes or the combination of both (Cuvelier, 1994).

Intraepithelial lymphocytes

T-Lymphocytes interspersed in the epithelium are called intraepithelial lymphocytes. They are components of the MALT and are predominantly CD8+ (Cesta, 2006). They are important in cell-mediated immune responses, in the regulation of secretory immunity and in the mediation of systemic tolerance (Gebert, 1996). They have been extensively studied in the intestines (Mahadeva et al., 2002; Chang et al., 2005). The presence of intraepithelial lymphocytes in the uterine tube has been previously demonstrated by immunoelectron-microscopic study (Otsuki et al., 1989) and they have proposed that they migrate via the basal lamina from the underlying follicles. In the present study, not only the presence of intraepithelial lymphocytes in the uterine tube epithelium but also their close association with dendritic cells and M cells has been demonstrated.

High endothelial venules

High endothelial venules (HEVs) are specialized postcapillary venules found in lymphoid tissues that support lymphocyte extravasation from the blood (Girard and Springer, 1995). They are lined by cuboidal epithelium. Recirculating lymphocytes migrate into peripheral lymphoid tissue through HEV (Duijvestijn and Hamann,1989). HEVs had been described in lymph nodes (Gowans and Knight, 1964; Farr, 1951; Farr and De Bruyn, 1975), Peyer's patches (Schoefl, 1972) and tonsils (Sordat et al., 1971; Indrasingh et al., 2002). Otsuki et al. (1989) have reported that HEVs are absent in the uterine tube. But in the present study, HEVs could be identified in the subepithelium of the post-partum uterine tube by electron microscopy. As HEVs are recognized to be the selective site for lymphocytic migration, their presence in the human uterine tube confirms the uterine tube as part of MALT.

In conclusion, the demonstration of various components of the mucosal immune system like Langerhans cells, M cells, intraepithelial lymphocytes and HEVs in the human uterine tube by electron microscopy indicates that the uterine tube is an integral part of MALT. The antigen-presenting cells in the human uterine tube involve both in immunostimulation while counteracting pathogens, and in immunotoleration in allowing successful fertilization. Our identification of the components of MALT in human uterine tube would result in further studies on the role of these cells in the female reproductive organs.

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