

Indurative Edema of the Prepuce Mimicking Phimosis, an Atypical Manifestation of Primary Syphilis.

Dear Sir or Madam,

We report the case of a 23-year-old married man from a rural area admitted to the emergency room of the Urology Clinic because of a marked edema of the free edge of the prepuce that was infiltrated, painless, and prevented retraction. The edema appeared 3 days earlier, without inguinal lymphadenopathy. As primary syphilis was suspected, the patient was referred to the Dermatology Department. Clinical examination did not reveal the presence of the partner's skin or mucosal lesions characteristic of primary or secondary syphilis, and no history of STD risk. The patient denied the presence of previous injuries to the genital area: the glans, coronal sulcus, or prepuce, and any other sexually transmitted infections. We conducted a non-treponemal venereal disease research laboratory (VDRL) test and a *Treponema pallidum* haemagglutination (TPHA) test for syphilis: both were negative. Non-steroidal anti-inflammatory therapy was administered *per os* and locally at admission. After seven days, the patient developed non-inflammatory bilateral inguinal lymphadenopathy, and during clinical examination we observed a slight reduction of the edema, which made visible discrete 10×10 mm erosions on the internal prepuce face (Figure 1a). Full blood count revealed leukope-



Figure 1. a) Discrete endured erosions on the internal prepuce face (Indurative edema-clinical aspect); b) A tough ulcerate chancre on the clitoris, and a typical hard chancre of the major labia.

nia ($2,686 \times 10^3 / \text{mm}^3$). At the request of the patient, who complained about the lack of satisfactory sexual intercourse and difficulty in maintaining proper local hygiene, we performed circumcision, which was useful in establishing the STD which caused the lesion (1-3). Tissue fragments were processed by standard histological methods and stained with hematoxylin-eosin (HE). Microscopic examination revealed marked ulceration of the mucosa on the inner surface. Adjacent to the ulceration, unkeratinized stratified squamous epithelium showed a marked hyperplasia with acanthosis. Underlying the ulceration was a rich inflammatory infiltrate consisting of lymphocytes, histiocytes, rare neutrophils, and numerous plasma cells. Plasma cells were distributed mainly perivascularly. Inflammatory infiltrate included nearly the whole thickness of the prepuce from the submucosa to the subcutaneous connective tissue. Along with inflammatory cells, an interstitial edema was noted, as well as dilated lymphatic vessels, small blood vessels with thickened walls, and endothelial swelling cells (Figure 2a, Figure 2b). Immunohistochemical investigation revealed a polyclonal inflammatory infiltrate consisting of CD3-positive T lymphocytes, CD20-positive B lymphocytes, and CD68-positive macrophages. Ki-67 proliferative index was expressed in about 10% of the inflammatory cells (Figure 2, c, d, e, f). The presence of ulceration on the inner face of the prepuce indicated a differential diagnosis with a list of possible causes: primary syphilitic chancre caused by *Treponema pallidum*, chancroid caused by *Haemophilus ducreyi*, *Zoon balanitis*, inguinale granuloma, and even insect bite reaction (4). The patient and his wife were clinically and serologically reviewed 28 days after the onset of the disease. Serological results were strongly positive in both the patient (VDRL 1/32 and TPHA 1/10240) and the wife (VDRL 1/16 and TPHA 1/5120). His wife presented with two specific symptoms of primary syphilis: a tough ulcerate chancre on the clitoris, and a typical hard chancre of the major labia (Figure 1b). We initiated the treatment with benzathil penicillin IM at a 4.8 million dose divided in two doses at a 7

day interval. Serological tests were performed at 9 and 12 months, and both the patient and the partner were negative.

Primary syphiloma is located at the entry point of treponemas (5), i.e. in the skin or mucosa that comes in contact with a blooming syphilitic lesion. Histological primary syphiloma or hard chancre is characterized by the presence of erosions or ulcers with psoriasiform hyperplasia of the epithelium. In the dermis there is a rich inflammatory infiltrate composed of lymphocytes, histiocytes, and numerous plasma cells as well as small blood vessels with thick walls and edematous and swollen endothelial cells. Obliterative endarteritis phenomena may occur, as well as induration due to the mucoid substance of the dermis (7). *Treponema pallidum* can be identified by silver staining – Warthin-Starry stain, immuofluorescence or immunohistochemistry, and dark-field examination of the lesion. When the entry point is on the inner face of the prepuce near the free edge, it generates a particular clinical manifestation of primary syphilis,

which is called indurative edema, characterized by particular structural features of the area. Indurative edema manifests as a marked edema of the free edge, discretely infiltrated, and painless, which causes the inability to retract the prepuce over the glans due to the enlarged prepuce (edema) without regional adenopathy. Due to the fact that at 10 days after onset erosion can be noticed at the free edge of the prepuce, induced by partial remission after treatment with anti-inflammatory drugs, indurative edema can be classified as an atypical form of hard chancre. Additionally, in indurative edema there is a polymorphic inflammatory infiltrate with segmented neutrophils, lymphocytes, histiocytes, and numerous plasma cells arranged mainly perivascularly as well as rich interstitial edema, especially in the chorion extended to the papillary dermis. It is determined by the specific histological prepuce structure in five layers, from the outer to the inner: epidermis, dermis, a thin layer of smooth muscle, lamina propria, and mucosa (7).

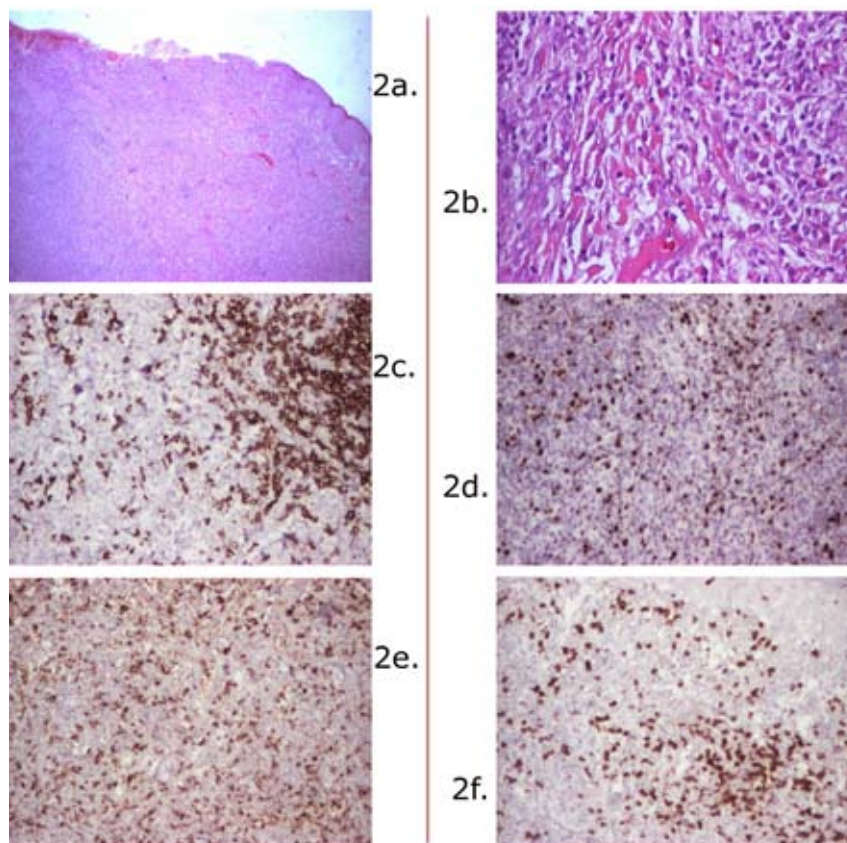


Figure 2. a) Ulceration of the mucosa on the inner surface - the ulceration of unkeratinized stratified squamous epithelium and a rich inflammatory infiltrate, Hematoxylin&Eosin staining, Ob. 2x; b) A rich inflammatory infiltrate consisting of lymphocytes, histiocytes, rare neutrophils, and numerous plasma cells, Hematoxylin&Eosin staining, Ob. 10x; c), d), e), f) Immunohistochemistry - a polyclonal inflammatory infiltrate: CD3-positive T lymphocytes (c), CD20-positive B lymphocytes (d), and CD68-positive macrophages (e). Ki-67 proliferative index was expressed in about 10% of the inflammatory cells (f), Ob. 10x

Previous absence of other mucocutaneous lesions in the genital area, the onset of indurative edema in the immunological window period, followed by subsequent positive specific serology of syphilis and the initial absence of syphilitic regional adenopathy with its appearance later in the development of indurative edema indicated the primary character of lesion. Indurative edema is rare in practice, and there are few references in the literature (8). In practice it is often confused with syphilitic phimosis that occurs later, as a complication of a hard chancre located in coronal sulcus or the inner surface of prepuce. Phimosis can be congenital or acquired due to numerous causes: most common are infections, diabetes, trauma, or local neoplasia (9). Syphilitic phimosis develop due to a dense package of loose connective tissue associated with a rich infiltrate in lymphocytes and plasma cells and the formation of new elements of connective tissue that give a retractile "collar-like" aspect that prevents retraction of the prepuce over the glans. Unlike indurative edema, in syphilitic phimosis regional lymphadenopathy is already present at the onset, serological reactions for syphilis are positive, especially TPHA, and the patient describes the corresponding lesion of hard chancre that preceded phimosis. An important criterion of clinical differential diagnosis for indurative edema is prepuce edema, and fibrosis in syphilitic phimosis.

Indurative edema is an atypical manifestation of primary syphilis with specific location at the prepuce, scrotum, and major labia. When located at the prepuce it may mimic a true phimosis if its free edge is impaired. This manifestation requires clinical monitoring as with any phimosis, especially those accompanied by edema, with reassessment in the next 3-4 weeks for serologic exclusion or confirmation of treponemal infection.

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