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Chapter 8

Effects of Tonsillectomy on Psoriasis and Tonsil Histology-Ultrastructure

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Additional information is available at the end of the chapter

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1. Introduction

Psoriasis is a chronic inflammatory disorder involving both cutaneous and mucous surfaces. Microscopic findings include a reactive abnormal epidermal differentiation, parakeratosis and elongation of rete ridges along with a characteristic mononuclear and neutrophilic inflammatory infiltrate.

Although several clinical variants of psoriasis are well recognized (i.e. guttate psoriasis, pustular psoriasis), the so-called plaque type is the most common type. It mainly affects the extensor limbs surface and the scalp with circular or oval red plaques variable in extention and duration.

Numerous studies indicate subclinical or recurrent streptococcal infection as a trigger or maintenance factor in the pathogenesis of psoriasis in children but although it is well known that guttate psoriasis may be precipitated by streptococcal infection, there is no firm evidence to support the use of antibiotics either in the management of established guttate psoriasis or in preventing its development following streptococcal sore throat. Although both antibiotics and tonsillectomy have frequently been advocated for patients with recurrent guttate Psoriasis or chronic plaque Psoriasis, there is to date no evidence that either intervention is beneficial. Few histological and no ultrastructural studies to date have directly investigated psoriatic effects on palatine tonsils.

The pathophysiology and etiology of psoriasis rest on different and poorly defined mechanisms and conditions mainly related to environmental and genetic factors, the latter related to disease susceptibility. Moreover, additional studies focused on the role of infections as well as

bacterial products, toxic or antigenic substances that may act as stimulating factors for polymorphonuclear leukocyte chemotaxis, cytokines and proteolytic enzyme production and T cell response.

The current pilot study attempt to investigate the role of infections in patients with psoriasis and chronic tonsillitis, evaluating the differences among those patients and a non psoriatic control group suffering from chronic tonsillitis, both groups having evidence of beta-haemolytic streptococcal colonization. Clinical data and histological/ultrastructural findings as well as literature data pertaining such a subject were taken into account.

Preliminary date are reported and discussed.

2. Background on tonsil immunology

The tonsil surface is usually covered by stratified squamous epithelium that envelops tonsils to form the crypts. There are generally some 20-30 crypts for tonsil. Within the crypt epithelium is not tightly arranged and presents macrophages, dendritic cells and lymphocytes to epithelial cells interspersed. Furthermore the wall contains cryptic cells micropores (M), which are tubulovescicular in nature and facilitate the internalization of the antigen. Under the epithelium it extends the interfollicular zone, rich in T cells. Moreover this is an area of antigen presentation by interdigitating cells, macrophages, and follicular dendritic cells. The germinal centers of lymphoid follicles are the locations of differentiation and proliferation of B cells.

Immune function itself begins with the effective internalization of the antigen from the pharynx to the tonsillar lymphoid tissue. After the antigen is placed inside a tonsil is processed and presented to T and B lymphocytes. The resulting interaction leads to terminal differentiation of B cells into antibody forming cells and the creation of T and B memory cells. The appropriate sensitization is required for effective immune function and there are multiple systems and many molecules that can induce functions of T and B cells in various extensions. This system works in concert, but, and it is important, the inappropriate reporting can lead to down-regulation of the immune responsiveness of T and B cells. It's therefore necessary to consider the different factors that can lead to modulation of the immune response.

The antigen is internalized in extra follicular areas of the tonsil passing through the M cells localized at the base of the tonsillar crypt. These tubulovescicular cells carry antigens in the tonsil [1]. Dendritic cells and macrophages are also found in the epithelium of cryptic wall. As the M cells they internalize the antigen; however they are also involved in antigen presentation to T cells in the extra follicular areas and the follicles of B cells [2].

Antigen presentation is a complex interaction between the antigen presenting cells and T and B lymphocytes. The first process the antigen and present it bound to the antibody in such a way as to interact with specific molecules on the cell surface of the lymphocytes. The principal antigen presenting cells are macrophages, interdigitating cells and follicular dendritic cells. The macrophages are present both in the epithelium of the crypts and in the germinal centers, as noted with the use of monoclonal antibodies (mAb) MAC 387 and CD68. MAC 387-positive

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cells were observed in the epithelium of the crypts, while CD68 in extrafollicular areas and germinal centers. These two types of macrophages represent a means for the signaling of B and T cells [3].

The exact nature of the macrophage-lymphocyte signal is not fully known; however it seems to involve a direct cell to cell contact in which the macrophage extends a cytoplasmic process that surrounds the lymphocyte. This interaction depends from the expression by the macrophage antigen MHC class II, which are expressed after activation by the interferon-γ. In addition to interaction with B and T cells, macrophages also interact with follicular dendritic cells through direct contact. Despite the foregoing discussion indicates that macrophages play an important role in antigen presentation, their role in the activation of lymphocytes has not been fully determined. Another antigen presenting cell, the interdigitating cell, that contains S-100 protein, is found more frequently in extrafollicular areas but was found in cryptic epithelium.

Unlike macrophages, it expresses the antigens MCH II without priming by interferon-γ. Such as macrophages, it is found in close contact with helper T cells and it is believed to present the antigen to in maturation T cells. The follicular dendritic cells, which contain the active C3b found on immune complexes, are present in germinal centers and in mantle zones. In these areas, the follicular dendritic cells distribute antigens to B cells, which in turn in germinal centers present the immunogen to T cells. The interaction of the follicular dendritic cell with the B cell can lead to the development of the B cell or a B cell memory, or in a cell secreting immunoglobulins [4].

Along with these antigen-presenting cells, other cells may play a supporting role in the activation of lymphocytes. The cells of the fibroblastic latex, for example, are found in the T cell areas and form a dendritic network [5]. The function of these cells is unknown; however fibroblasts treated with interferon-γ have shown to express antigens of the major histocompatibility complex on their surface. With other signals fibroblasts can play a role in increasing the T cell response to antigenic stimulation.

The successful activation of T and B lymphocytes is the result of complex interactions between 1) the antigen presenting cells and lymphocytes, 2) the accessory cells and lymphocytes, and 3) the T and B lymphocytes. These interactions occur by direct contact or via cytokines. The direct interaction between antigen presenting cells and T cells involves multiple connections[5]. There are numerous determinants of T cells and their respective ligands of antigen presenting cells in tonsil tissues. A main surface molecule of lymphocyte is the determinant C3, structurally related to the T cell receptor (TCR) and subjected to tyrosine phosphorylation of one of its chains upon interaction of the TCR/CD3 complex with the antigen.

The T cell activation results in an increase of intracellular calcium. The association of other ligands presenting cells with antigen determinants surface of T cells involves an increase in the concentration of intracellular calcium and acts synergistically with the CD3 mediated events in the increasing activating T cell. One of these determinants, CD2, is considered to play a role both in cell to cell adhesion that in the activation of T cells. On the other hand CD4 and CD8, when bound to the antigen presenting cells, can produce an increase of intracellular calcium but not of T cell activation, as revealed by the production of interleukin-2 (IL-2) or

from induction of cell proliferation. And interestingly, if the interaction with the antigen leads to the association of CD4 and CD8 with CD3, then the binding determinants on antigen-presenting cells induces T cell activation. Another surface molecule, CD54 (decay-accelerating factor DAF), does not increase the intracellular calcium per se, but the cross-linking of these molecules can induce T cell proliferation. Furthermore, the cross-linking of CD54 and CD3 results in an increase in calcium concentration induced by CD3 as well as the proliferation of T cells. Together with T cell activation, the activation of B cells is a necessary component of a proper immune function. Germinal centers in the follicular dendritic cells are probably the most important antigene presenting cells for B cells. They carry a large amount of antigen in the immune complexes containing complement. The antigen-antibody complexes are connected to follicular dendritic cells via complement and Fc receptors. This complex of macromolecules is incorporated in the ISCOMs (immunostimulating complexes), corpuscles linked to the membrane coated with immune complexes, which are released into the intercellular space, where the B cells are joined. The i Interaction of ISCOMs bounded antigen with the B cell is incremented because the proteins of the surface of B cells interact with both the antigenic determinants and the complement factors. This cross-linking of surface receptors of B cells leads to activation of the B cell. The involvement of complement factors can lead to the formation of terminal complement complex, which apparently did not cause any damage. The terminal complement complexes can lead to a release of inflammation mediators and mild edema. This intratonsillar edema facilitates the dispersion of ISCOMs and increases the chance of contact with B cells and their activation. B cells are further activated by helper T cells of tonsil via cell to cell contact and then the antigen presented to B-cells is further processed by them and thus presented to T cells in the context of class II molecules of human leukocyte antigen (HLA).

Together with the cell to cell interactions the activation of immune system is mediated by cytokines. At least 19 different cytokines are found in the tonsils of patients with infectious mononucleosis, or recurrent tonsillitis [6]. Cytokines are easily found in all areas of surface epithelium of the germinal center. The IL-2 is well known for its ability to increase the lymphocyte activation. The follicular dendritic cells induce the production of IL-6 and the clonal proliferation of T cells. Cytokines are also involved in the regulation of the production of IL-1, in the change of immunoglobulins in all IgG subclasses, in the production of IgA and induction of the Bcl-2 gene, which prevents the apoptosis of B immune activated lymphocytes.

The formation of an appropriate immune response, therefore, depends on a myriad of complex interactions between cryptic epithelial cells, macrophages, interdigitating cells, follicular dendritic cells, T cells, B cells and cytokines. The successful interactions lead to the production of activated B cells, which enter the bloodstream and at the same time are associated with the glandular tissue and the lamina propria of the epithelium of the upper respiratory tract [7] or differ locally in producing immunoglobulins cells. The IgA is the main immunoglobulin produced in the mucosa-associated lymphoid tissue (MALT) and in the areas of the upper respiratory tract is favored the production of IgA 1. In tonsils and adenoids, as in the rest of the MALT, are prevalent the IgG immunocytes and IgA-producing cells are around the 30% -35%. The IgA is a dimer, whose molecules are linked by a chain J [7].

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In tonsils, adenoids unlike, dimeric IgA do not increase the range of secretory passage through the epithelium. While both IgA and IgG antibodies in the secretions pass directly through a link with pharyngeal epithelial cells. This is incremented by inflammation.

The infection leads to chronic and recurrent tonsillar hyperplasia and /or nodularity. Morphologic features include expansion of lymphoid follicles and prominent germinal centers formation, with intact mantle zone and mixture of cell types including B lymphocytes and T lymphocytes as well as histiocytes and plasma cells. Polymorphonuclear can be found within the epithelium and as aggregates within the crypts along with bacteria. Furthermore, multinucleated giant cells may occur during viral related infections.

Chronic inflammation initially involves an increase of reticular epithelialium. Later, however, the crypts become coated by squamous epithelium, devoid of M cells, which facilitate the entry of the antigen [8]. This can lead to a reduction in the amount of processed antigen for presentation to T cells. In addition, patients with tonsillar focal infection have a minor amount of tonsil follicular dendritic cells in the lymphoepithelial symbiosis. Since multiple interactions are necessary for proper T-cell response, the reduced antigen presentation may result in the suppression of the immune response. It has been shown that the suboptimal T cell signaling involves a partial activation and that partially activated T cells can produce cell surface receptors for cytokines but cannot proliferate. Such partial activation may currently lead to tolerance, inhibition of responsiveness and defective production of IL-2.

Bernstein & al. [9] have shown the decreased production of IL-2 in 34 patients who underwent adenoidectomy or adenotonsillectomy. In these patients, it was found that T cells of adenoids weakly support the production of B cells of the major isotopes of immunoglobulins. This was attributed to the reduction of the production of IL-2, in response to stimulation of both mitogens and specific antigens, by means of lymphocytes of adenoid and tonsil, in comparison with peripheral blood lymphocytes. Interestingly this reduction in the production of IL-2 was observed in the context of a very spontaneous lymphoproliferative activity. The authors suggested that the continuous bottom stimulation of tonsillar and adenoidal lymphocytes could lead to an increase in non-stimulated proliferative activity and a decrease of the response to specific antigenic challenges.

Even Koch and Brodsky [10] examined lymphocyte activation in patients with chronic tonsillitis. Noticed a decreased of proliferative response to stimulation by H. influenzae type B and S. pyogenes in the pathological tonsils than normal. In addition, after stimulation, the death rate of tonsillar lymphocytes was accelerated. Their observation suggests that the lymphocytes of pathologic tonsils become refractory or tolerant to immune activation by certain pathogens associated with chronic tonsillitis. This result was further supported and extended by other Authors who have examined the response of the tonsillar and peripheral blood lymphocytes to mitogen and antigenic stimulation. They found that, while the basal mitogenic activity was high, the response to stimulation in these two lymphocyte populations was weakened. This reduction in response was attributed to the continuous release of immunosuppressive factors, and the resumption of the proliferative response after tonsillectomy.

So in certain situations hyperplastic tonsils can be seen as immunocompromised organs that may reduce the total efficacy of the local immune system. Patients with recurrent tonsillitis are

also deficient in B cells, perhaps for a decrease of IL-2 above mentioned or other additional changes in the profiles of the lymphokines produced by antigen-presenting cells and T cell subsets. Such changes may lead to a reduced retention of B-cell clones memory and a reduced production of secretory IgA.

This was evidenced by the reduced generation of B cells expressing the J chain in children with recurrent tonsillitis. Another important cell in the immune response is the neutrophil, which engulfs and destroys opsonized microorganisms. Chronic infections are acting negatively on neutrophil chemotactic function. The neutrophil function was studied in 17 patients between the ages of 4 and 11 years with chronic tonsillitis and adenoid hypertrophy. In such patients, chemotaxis was significantly lower compared to controls. The evaluation repeated 10 days after surgery showed no significant differences between the two groups, but the increase in the chemotactic response of neutrophil function after surgery was significant compared to preoperative values [11].

The chronic effect of adenotonsillectomy on immunoglobulins was studied at tonsil and peripheral blood. Several changes are induced by chronic, and some may be related to the presence of bacteria typically observed in adenotonsillar infections. As already stated, IgG and IgA are the primary antibodies produced in response to antigenic challenge, however is to be noted that the cells producing IgD are more prevalent in the MALT that in the gut associated lymphoid tissue [12]. This can achieve the stimulation of B-cell reserve, which express IgD, by H. influenzae and M. catarrhalis. These bacteria, which frequently colonize the upper aerodigestive tract, produce a binder IgD factor that has a cruciate connection with the IgD and with the molecules of class I human leukocyte antigen (HLA). This determines a polyclonal stimulation of the proliferation of B cells and results in an increased production of IgD and a preferential production of secretory IgA1 (SIgA1) above the production of IgA2.

The production of IgD and the preferential production of IgA1 have important implications for the local immune response. First, IgD cannot act as secretory immunoglobulin. So the cells directed to differentiate in the production of these immunoglobulins are actually being removed from the immune globuline-producer cellular pool. Secondly, the H. influenzae produces a protease that cleaves IgA1. Even St. pneumoniae and Neisseria meningitidis produce this protease. Thus these bacteria, which are often found in patients with chronic adenotonsillitis, have developed both a mechanism for guiding the antibody production to the IgA1 and a mechanism for cleaving this product with specific protease [13].

These modifications of immunoglobulin may be related to the common finding of immunoglobulin levels increased in the peripheral blood of patients with chronic tonsillitis. Significant elevations of IgG, IgA, IgM and IgE were found in patients with chronic tonsillitis. After tonsillectomy, these values return to normal [14]. This apparent paradox of increased immunoglobulin levels in patients with chronic infection can be explained by the studies discussed above on T and B cell. Given the constant stimulation of the immune system in patients with chronic adenotonsillitis, there is a bottom elevation of mitotic activity and antibody production. However, in response to stimulation by specific bacteria, the production above this baseline level is limited, as shown by the decrease of the activity of both mitogenic tonsillar

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lymphocytes and of those in the peripheral blood. Can also be a concomitant inability to increase the production of specific antibodies in response to specific infectious agents.

Kurono & al. [15] have illustrated the latter point by examining the levels of sIgA and the adherence of S. pyogenes cells in the nasal mucosa. Secretory IgA inhibit bacterial adherence to mucosal cells attaching to the surface and directly interfering with bacterial adherence to the epithelium of the antigenic component of the surface of the bacterium. In their study of 29 patients with chronic sinusitis the Authors showed high levels of sIgA compared to 25 controls. Nevertheless the bacterial adherence to the nasal mucosa was increased in patients with chronic sinusitis. It appears from these results that, in spite of the immune system can produce a great quantity of immunoglobulins, there may still be a decreased activity in response to specific antigens. A similar situation may exist in patients with chronic tonsillitis, but lack specific data.

The previous discussion emphasizes the multiple immune defects that may be present in patients with chronic tonsillitis. It may be noted that in these patients may present a cycle of infection which involves epithelial modifications responsible for decreased antigen presentation and immunity function which in turn lead to further infection. Other influences can further reduce the immune response. What factors are the causative agents and if are simple or associated factors has not been fully delineated.

3. Patients and methods

A total of 13 patients with psoriasis and recurrent tonsillitis subjected to tonsillectomy in the Department of ENT-Maxillofacial Surgery, San Giovanni Bosco Hospital, Turin, Italy, between March 2003 and August 2010 were enrolled in this study (Group 1). In addition, 9 patients with recurrent tonsillitis and without psoriasis subjected to tonsillectomy between June 2002 and September 2010 were enrolled in this study (Group 2). The diagnosis of psoriasis was confirmed by typical clinical findings and histopathological examination. The data were retrospectively reviewed to assess the epidemiological and clinical features.

Patients with psoriasis (Group 1) were further divided into two subgroups: patients without improvement of the psoriasis symptomatology (subgroup A, 4 patients) and patients with prolonged or temporary improvement of psoriasis symptomatology after tonsillectomy (subgroup B, 9 patients).

Eligibility requirements for both groups included a diagnosis of recurrent tonsillitis with none of the following other conditions: clinical history of allergy (alimentary, cutaneous or respiratory tract allergies), chronic respiratory pathologies (nasal septum deviation, hypertrophic rhinopathy, asthma, chronic sinusitis), surgical or clinical rhinopharyngeal and oral treatments (adenoidectomy, nasal polyps surgery, periodontal or peritonsillar abscesses drainage, dental or periodontal surgery).

Eligibility requirements for psoriasis group included a diagnosis of psoriasis made by a dermatologist, their disease course was followed for at least 2 years and their disease severity

assessed by the Psoriasis Area and Severity Index (PASI). PASI is the standard method for evaluating changes in the extent and activity of this disease [16]. Improvement was evaluated according to at least 50% PASI score reduction. A PASI score reduction of at least 50% (PASI 50) is considered as clinically meaningful improvement [17].

The participants were evaluated clinically at study entry and after every 6 months.

The diagnosis of recurrent tonsillitis and eligibility for tonsillectomy was made according with the Italian Guidelines on the clinical and organisational appropriateness of tonsillectomy and adenoidectomy [18,19].

National guidelines issued in 2003 restricted the surgical option mainly to: children with significant obstructive apnea (adenotonsillectomy), children with recurrent otitis media and ventilation-tube placement or with chronic/recurrent sinusitis and failure of appropriate antibiotic therapy (adenoidectomy), children and adults with severe acute recurrent tonsillitis (tonsillectomy).

In those Guidelines it is suggested that tonsillectomy be limited to children and adults with recurrent acute bacterial tonsillitis of proven severity, meeting the following criteria:

–Five episodes of tonsillitis per year;

–Episodes that are disabling and prevent normal functioning; and

–Symptoms lasting at least 12 months.

The patients were all examined for tonsillar remnants at the end of the study and no tonsillar remnants could be detected in any patient of the study after the surgical intervention.

There were not alcohol drinkers. Each case was characterized by age, presenting signs and symptoms, and mean duration of clinical symptoms antedating clinical diagnosis and tonsillectomy. The patients had a full physical examination, complete blood counts and clinical laboratory tests including leucocyte count.

The number and duration of recurrent tonsillitis episodes as well as response to antibiotic treatment and history of medical conditions were recorded. Such clinical informations gathered on each patient were further outlined by considering available medical records, parents report and, when possible, by contacting each respective attending physician.

After a period of clinical examination and data recording, patients underwent tonsillectomy. Tonsils were removed by dissection and haemostasis was controlled with suction cautery, pressure and/or suture ligature. Patients follow-up revealed no post-operative complications.

Tonsils from both psoriatic and non psoriatic groups were collected, washed in buffered saline, measured along the three dimensions and immediately processed by conventional methods within half an hour after surgery.

In particular, perpendicular sections to the long axis of each tonsil were fixed in 10% neutral-buffered formalin, routinely processed for histology and stained with haematoxylin and eosin, periodic acid-Schiff (PAS) and Weigert van Gieson. The following parameters were recorded

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for the entire tonsillar area: surface and cryptic epithelial changes, follicles, subepithelial and interfollicular compartments.

On the contrary, small fragments (5-mm-thick) immediately collected after removal from the surface of each tonsil were fixed in 2% phosphate-buffered glutaraldehyde, post-fixed in osmium tetroxide, dehydrated with increasing concentrations of ethanol, dried in a critical-point apparatus under CO2, and examined in a Hitachi emission field scanning electron microscope (SEM) (Hitachi Ltd., Tokyo, Japan) at 25 kV. The morphology of surface and cryptic epithelium, and specialized surface cells was analysed.

Light and SEM examinations were blinded performed without knowledge of the clinical history and patient's condition.

4. Results

The 13 patients with psoriasis - 6 males and 7 females - aged 9 to 46 years were followed up 2 to 5 years after tonsillectomy. The subgroup A consisted of 1 male and 3 female patients suffering of guttate (2 patients) and chronic plaque psoriasis (2 patients). The subgroup B consisted of 5 males and 4 females suffering of guttate (6 patients) and chronic plaque psoriasis (3 patients). Duration of psoriasis varied from 5 to 24 years in subgroup A and from 4 to 13 years in subgroup B. Improvement duration in the subgroup B varied from 6 months to 5 years. The 9 patients without psoriasis - 1 male and 5 females - aged 9 to 35 years.

Clinical data regarding patients with psoriasis and recurrent tonsillitis (Group 1), subgroups A and B are reported in Table 1 and Table 2 respectively, whereas table 3 shows clinical data of the patients with recurrent tonsillitis and without psoriasis (Group 2).

Patients with psoriasis and recurrent tonsillitis Group1, Subgroup A (No improvement after tonsillectomy) Improvement: absent or < 50% improvement of PASI score							
Patients	**Sex**	**Age**	**Number of annual tonsillitis**	**Duration of psoriasis**	**Follow-up**	**Type of psoriasis**	**Improvement duration / PASI score improvement**
1	F	46	8	24 years	4 years	Guttate psoriasis	18 months 30%
2	F	31	5	22 years	5 years	Chronic plaque psoriasis	No improvement
3	F	9	5	5 years	2 year	Chronic plaque psoriasis	No improvement
4	M	11	6	7 years	5 years	Guttate psoriasis	No improvement

Table 1. Clinical data of the patients with psoriasis and recurrent tonsillitis with no improvement after tonsillectomy: Subgroup A of Group 1.

Patients with psoriasis and recurrent tonsillitis Group 1, Subgroup B (Improvement after tonsillectomy) Improvement: = or "/> 50% improvement of PASI score							
Patients	**Sex**	**Age**	**Number of annual tonsillitis**	**Duration of psoriasis**	**Follow-up**	**Type of psoriasis**	**Improvement duration / PASI score improvement**
1	F	35	5	7 years	4 years	Guttate psoriasis	4 years/ 50%
2	M	12	6	8 years	3 years	Chronic plaque psoriasis	6 months 90%
3	M	22	7	7 years	2 Years	Chronic plaque psoriasis	12 months 50%
4	M	10	6	6 years	2 years	Guttate psoriasis	6 months 75%
5	M	12	7	5 years	3 years	Guttate psoriasis	12 months 75%
6	M	9	5	5 years	5 years	Guttate psoriasis	3 years 90%
7	F	11	7	5 years	5 years	Guttate psoriasis	18 months 75%
8	F	10	5	4 years	3 years	Chronic plaque psoriasis	6 months 100%
9	F	18	5	13 years	5 years	Guttate psoriasis	5 years 50%

Table 2. Clinical data of the patients with psoriasis and recurrent tonsillitis with improvement after tonsillectomy: Subgroup B of Group 1.

Patients with recurrent tonsillitis and without psoriasis			
Patients	**Sex**	**Number of annual tonsillitis**	**Age**
1	M	7	13
2	F	6	12
3	F	6	18
4	M	6	29
5	M	5	11
6	F	5	10
7	F	7	9
8	F	5	35
9	M	5	18

Table 3. Clinical data of the patients with recurrent tonsillitis and without psoriasis: Group 2.

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Clinical findings demonstrated clear differences between psoriatic and non-psoriatic group, the former showing further differences between subgroup with long-term or short-term improvement of psoriasis symptoms (subgroup B) and subgroup with no-improvement after tonsillectomy (subgroup A).

Psoriasis had long term improvement (PASI = OR < 50%) after tonsillectomy in two out of the eight patients (25%) with guttate psoriasis and had a short-time improvement in four patient (50%). Three out of five patients with chronic plaque psoriasis (60%) had a short-time improvement, two (40%) were unchanged.

On the other hand, light microscopy and SEM findings showed minimal differences between the control and both psoriatic subgroup A and B.

Histology of tonsils revealed well-known morphological features of reactive and hyper-plastic pattern in both psoriatic and non-psoriatic groups. Secondary follicles with well-defined germinal centres and mantle zones, irregular and enlarged follicles and florid follicular hyperplasia were usually observed. Clear follicular expansion and irregularity as well as evident infiltration of lymphoid cells in the tonsillar crypt epithelium, along with irregularity of the epithelial wavy basal membrane and epithelial basal profile were noted in two cases from psoriatic subgroup B: case 6 and case 9.

Interstitial fibrosis along with a dense collagen matrix seemed more evident in both A and B psoriatic subgroups compared to non-psoriatic patients and were sometimes associated with a variable degree of stromal oedema and haemorrhages. A fine small blood vessels network was clearly observed in both groups beneath the epithelial surface and in association with the reticulated epithelium as finger-like projections surrounded by connective tissue, with hyperaemia and extravasated red blood cells. Blood vessels thickening or microscopic features of vasculitis were not observed in either groups.

Tonsillar crypt epithelium showed cellular degeneration, variable degree of thickness and intercellular spongiosis or micro-vescicular formation, with no histological distinctive pattern or significant quantitative differences between psoriatic and non-psoriatic patients. Both groups showed some dilated and pseudocystic crypts lined by squamous epithelium and filled with squamous debris along with a mixture of lymphocytes, neutrophils and desquamated epithelial cells. Bacterial aggregates were sometimes observed near or within the crypt lumen in both groups.

Scanning electron microscopy correlated with histology and revealed the surface epithelium consisting of squamous and sometimes keratinized cells in an irregular pattern of microridges and sometimes rod-like elements, referring to bacteria, adhering to the epithelium, in both psoriatic and non-psoriatic patients (Fig.1). A fine meshed and sometimes cerebroid-like net of the epithelial surface was observed. Specialized surface cells with short microvilli were noted close to lymphocytes or macrophages. Lymphoid cells were frequently observed near the crypt lumen along with surface cellular debris, detached epithelial cells and scattered bacteria (Fig. 2).

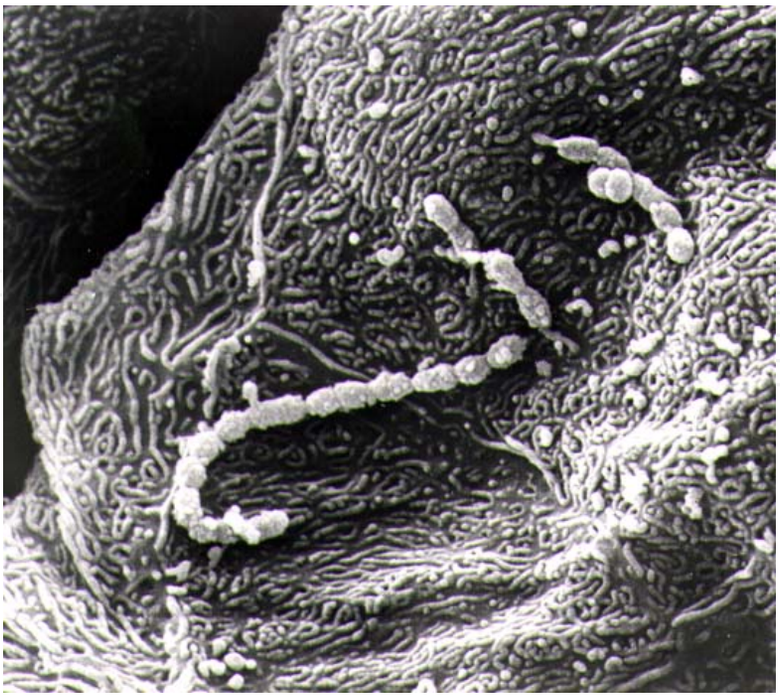

Figure 1. Particular of the surface tonsillar epithelium(patient 4 of Group 1, Subgroup A): rod-like elements, referring to bacteria, adhering to the epithelium, in a more or less intact area (scanning electron micrograph, x1000).

Figure 2. Particular of the surface tonsillar epithelium (patient 6 of Group 1, Subgroup B): accentuated reticulation of epithelial elements; crypts are hard to find, often masked by debris, mucus and epithelial desquamation (scanning electron micrograph, x1000)

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5. Discussion

Recently was postulated that psoriasis is a genetic based chronic cutaneous inflammatory disorder, involving several genes encoding proteins involved in epidermal differentiation and immune, inflammatory and pathogenic responses, in combination with microbial environmental factors. The importance of the microbial environment is fundamental to demonstrate the correlation between genetic ground and clinical manifestation, because these agents may function as triggers for immunological dysregulated responses, especially in a particular context in which there is an impaired capacity of barrier organs to regulate microbial flora and prevent entrance of bacteria, viruses and fungi [20].

The association between streptococcal infections and guttate psoriasis or plaque psoriasis and has been known for a long time and is well-documented.

The mechanisms, however, are still a matter of investigation and several findings indicate a possible role for various bacterial proteins and/or toxins serving as superantigens.

Psoriasis exacerbation has been linked with skin and/or gut colonization by Staphylococcus aureus, Malassezia, and Candida albicans. The role, if any, of viruses (papillomaviruses, HIV, and endogenous retroviruses) present in lesional skin is at present unknown. The use of various drugs, such as lithium, β-blockers, antimalarial agents, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors, has also been associated with induction or worsening of disease in psoriatic patients [21].

The triggering of guttate psoriasis was initially associated with Lancefield group A streptococci (S pyogenes), but streptococci of groups C and G have also been isolated from the tonsils of patients with guttate psoriasis. Group A (C and G) streptococci express one of several antigenically distinct M proteins on their surface; however, no association has yet been found between particular M serotypes and the triggering of guttate psorisis by group A streptococci [22,23].

Honig [24] found an association between perianal streptococcal dermatitis and guttate psoriasis, while Rasi & al. [25] found the association between perianal streptococcal dermatitis and plaque-type psoriasis.

Based on epidemiological data McFadden & al. [26] postuled the natural selection of psoriasis, whose immunological pathways may confer protection against mortality during epidemics of invasive streptococcal infections, heightened efficiency in internalizing and allowing carriage of streptococci as well as predisposition to the development of psoriasis.

The first report that the onset of guttate psoriasis is often preceded by throat infections with b-haemolytic is due to Winfield in 1916 [27]. The link between psoriasis and streptococcal infection is probably explained by the 'superantigen theory'. The streptococcus carries a protein called the M-protein which allows it to act as a superantigen. Superantigens are bacterial or viral products that can bypass normal immunological pathways and cause powerful stimulation of the immune system. This results in the production of T-lymphocytes (white blood cells) which have been shown to be central to the development of psoriasis.

Streptococcal throat infections are related to the incidence of psoriasis onset is also highest between the ages of 11 and 20 years.

In children, the first manifestation of psoriasis is commonly drop- like with sudden onset after an infection of the upper airways. The guttate psoriasis is localized predominantly in the exposed parts of the body, such as the face and limbs. The lesion has a diameter of about 1-3 cm, in color from pink to red, with the scales overlying gray or silver. The frequency of this clinical variety, characterized by acute onset and guttate lesions, decreases with increasing age, so as to become rare in the adult, when the predominant form is plaque psoriasis.

The plaque psoriasis, as opposed to the drop-like form, prefers the surfaces of the skin at bony eminences, such as the knuckles, elbows and knees. Approximately 30-50% of children with psoriasis has a family history of the disease. The psoriasis is in fact more often associated with antigen CW6 of class I HLA. The principal gene of susceptibility to psoriasis appears to resides on chromosome 6, which is just the home of the HLA complex HLA I and II. But probably many other genes are involved, as there are also external environmental influences, which recently were shown to be very important.

Streptococcal throat infections are most common around puberty and the incidence of psoriasis onset. Psoriasis is not uncommon in pediatric age group, becouse 27% of cases manifest before the age of 16 years; moreover, psoriasis represents 4.1% of all dermatoses seen in children under the age of 16 years [28].

Literature data on juvenile psoriasis are shown in table 4.

Author	N° of patients	Male:female ratio	Peak age of onset (years)	Infection precipitating factor	Plaque type incidence
Morris 2001 [29]	1262	1:1.14	8	-	34%
Kumar 2004 [30]	419	1.09:1	6-14	6.6%	60.6%
Kim 2010 [31]	30	1:2.33	8-11	43.4%	63%
Seyhan 2006 [32]	61	1:1.65	6-11	14.8%	54.1%
Dhar 2011 [33]	419	1.25:1	6-10	28.5%	60.6%
Kwon 2012 [34]	358	1.06:1	10-11	-	67%

Table 4. Literature data on juvenile psoriasis

In a previous retrospective study, about 30% of patients with chronic psoriasis reported that they had noted worsening of their disease in association with sore throat [35]. The same Author successively observed a significant exacerbation of chronic plaque psoriasis only if streptococci were isolated and the patients were assessed 4 days or later after the onset of sore throat. No difference was observed between groups A, C or G streptococci in this respect.

Consecutively psoriasis patients should be encouraged to report sore throat to their physician and that early treatment of streptococcal throat infections might be beneficial in psoriasis[36].

According to Camisa [37]: "In general new onset guttate psoriasis related to streptococcal infection involutes rapidly within a four week period with antibiotic treatment. In patients

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with chronic psoriasis who develop a guttate exacerbation, empiric treatment with antibiotics is indicated".

Furthermore Farber [38] stated: "prevention and early treatment with appropriate antibiotics administered at the onset of upper respiratory infections in children with psoriasis may be able to block the appearance of acute guttate psoriasis".

A study confirms the strong association between prior infection with Streptococcus pyogenes and guttate psoriasis but suggests that the ability to trigger guttate psoriasis is not serotype specific [23].

The usefulness of early treatment of streptococcal infections for childhood psoriasis was demonstrated with a study about relationship between anti-streptolysin O (ASO) titers and the clinical features of psoriasis.

The Authors also stated that the childhood psoriasis patients with high ASO titers had guttate psoriasis more frequently than patients with normal ASO titers. In children with plaque-type psoriasis, psoriasis area and severity index score was increased in the high ASO titer group than normal ASO titer group [31].

In literature was also stated the efficacy of tonsillectomy in the treatment of psoriasis [39-42].

Literature data on the employment of tonsillectomy for psoriasis improvement are shown in table 5. Unfortunately for some work has not been possible to find the full bibliographic data.

Wilson et al. (2003) [55] evaluated 27 retrospective and 28 prospective uncontrolled studies on effect of tonsillectomy on psoriasis and founded 32% and 53% cleared percentages respectively.

Relapse of the psoriasis often occurs within 2 years of tonsil removal, probably due to colonization by streptococci of other lymphoid tissues in the upper respiratory tract.

Hone & al. in 1996 [40] investigated 13 patients with either recurrent guttate psoriasis or chronic plaque psoriasis exacerbated by tonsillitis. In this group, psoriasis cleared completely after tonsillectomy in five of six patients with guttate psoriasis and two of seven with chronic plaque psoriasis.

Rosenberg & al. [50] reported clearing of psoriasis in nine of 14 patients (all of whom had evidence of streptococcal colonisation) following tonsillectomy.

McMillin & al. [41] found that two children with recurrent streptococcal pharyngitis or tonsillitis complicated by recurrent guttate psoriasis were completely free of psoriasis 16 months after adenotonsillectomy.

Despite those assertions, a recent Cochrane review [56] concluded: "although it is well known that guttate psoriasis may be precipitated by streptococcal infection, there is no firm evidence to support the use of antibiotics either in the management of established guttate psoriasis or in preventing the development of guttate psoriasis following streptococcal sore throat. Although both antibiotics and tonsillectomy have frequently been advocated for patients with

Author	N° of patients	Age	Type of psoriasis	Cleared or improved rate	Follow-up
Kogon 1960 [43]	-	-	-	-	-
Whyte 1964 [44]	3	15-23	Guttate	~100% cleared	1 year
Cepicka 1967 [45]	92	-	-	61% cleared	2-5 years
Stukalenko 1967 [46]	3	-	-	-	-
Lukovskii 1970 [47]	57	-	-	89% improved	-
Nyfors 1976 [39]	74	4-33	Vulgaris	32% cleared	7-204 months
Saita 1979 [48]	2	7-11	Guttate	~100% cleared	-
Hone 1996 [40]	13	6-28	6 Guttate 7 Chronic Plaque	83% Guttate cleared 28% Chronic plaque cleared	6-52 months
Kataura 1996 [49]	35	-	Vulgaris	49% cleared	3 months
Rosenberg 1998 [50]	14	-	-	64% cleared	-
McMillin 1999 [41]	2	5-11	1 Guttate 1 Severe	~100% cleared	16 months
Ozawa 1999 [42]	385	-	Generalized pustular	16% cleared	-
Takahara 2001 [51]	7	9-46	-	42% cleared	2-9 years
Prasad 2005 [52]	13	5-36	-	75% improvement SAPASI score	-
Diluvio 2006 [53]	3	21-33	Ch. Plaque	~100% cleared	3 years
Thorleifsdottir 2012 [54]	29	19-54	-	86% cleared (30-90%)	2 years

Table 5. Literature data on tonsillectomy for psoriasis treatment.

recurrent guttate psoriasis or chronic plaque psoriasis, there is to date no good evidence that either intervention is beneficial".

Thorleifsdottir & al. [57] suggested that psoriatic patients after tonsillectomy has at least a temporary beneficial effect on chronic psoriasis, and is associated with a striking reduction in the frequency of circulating skin-homing CD8+ T cells that are specific for peptides with amino acid sequences that are present in both streptococcal M-proteins and human keratins. These amino acid sequences might therefore represent antigen determinants that are relevant in psoriasis. In a successive study the same Author [54] stated that there is a close correlation between the degree of clinical improvement in individual patients and reduction in the frequency of peptide-reactive skin-homing T cells in their circulation and therefore tonsillectomy may have a beneficial effect on chronic psoriasis because the palatine tonsils generate effector T cells that recognize keratin determinants in the skin. According to this Author: "identification of circulating T cells that respond to homologous M protein and keratin determinants in patients with treatment-induced remission may help to identify primary autoepitopes that might be targeted for highly specific immunotherapy for psoriasis".

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A recent European expert group consensus [58] stated that: "in cases where there is a positive streptococcal swab and more than three recurrent infections, tonsillectomies are indicated for patients with plaque or guttate psoriasis".

Perhaps, according to Sigurdardottir [59]: "Some patients with recalcitrant guttate or chronic plaque psoriasis, particularly those with early-onset psoriasis that is exacerbated by streptococcal tonsillitis appear to have long-term remissions following tonsillectomy".

Some authors have highlighted the differences from the histological point of view between the tonsils of patients who achieved an improvement of psoriasis after tonsillectomy, compared to the tonsils of patients who did not obtain this improvement [51]. The above mentioned differences are related to the expansion of the T cell-nodules area and the increasing of the number of apoptotic cells in tonsil from patients with psoriasis compared to those with recurrent tonsillitis. The Authors suggested that histological evaluation may be helpful in estimating the effectiveness of tonsillectomy.

6. Conclusion

Association between psoriasis and streptococcal pharyngitis has been recognized for many years. To explain the possible association between drop elements of the psoriasis and infections of the pharynx by Streptococcus is necessary to focuses on immunology of the skin.

In the skin there are 3 types of antigen-presenting cells:

a. the Langerhans cells

b. the dermal dendrocytes

c. the tissue macrophages

Their function is to attack the proteins, to insert their fragments (epitopes) in complex MHC I and II, which are present on the cell surface and to present these antigens to T-cell receptors.An activation signal occurs when the B7 on the surface of antigen presenting cells binds to the CD28 receptor of T cell The thus activated T cell begins to produce cytokines. In psoriasis T cells of the skin are primarily CD8 + cells in the epidermis and CD4 + in the dermis. Cytokines are represented by interleukin 2 (IL-2) that activate other T cells and the gamma interferon, which enhances the expression of cell surface antigens of the MHC [60].

Superantigens are presented by antigen presenting cells without the need of a preparation and presentation in the MHC complex. The superantigens strep attach directly to the V region of the beta-2 CD4 + T cells, which preferably harbored in the skin. The stimulation of the superantigen activates more than 10% of all lymphocytes exposed, while the conventional antigens, expressed on the T cell receptors, stimulates only about 1 in 10,000 T cells.

These activated T cells, mainly CD4 +, they release a large number of cytokines, including IL-2, interferon gamma and growth factors, which attract T cells and CD8 + T cells of the epidermis. The stimulation of the population of suprabasal keratinocytes, by the cells transiently multi-

plying, determines an hyperproliferation, increases the resistance to apoptosis and increases the expression of keratin, including the keratin 14 of the skin. Recent information suggests that there is a strong homology between the keratin 14 of the skin and M-6 of Streptococcus.

So there can be a large population of T cells (V beta-2, CLA +), that lodge in the skin, which are activated by the superantigen Streptococcus; between these some T cells responding to the antigen M-6 of the Streptococcus, that cross-reacts with cutaneous keratinocytes 14. This cascade of events may be the cause of the injury thickened and red, that dermatologists and pediatricians recognize as guttate psoriasis.

In short, the processes that lead to the appearance of guttate psoriasis in susceptible individuals after Streptococcus infection can be done in two stages.

The streptococcal superantigen in genetically susceptible individuals actives most of the CD4 + T cells that lodge in the skin, as the target organ. These activated T cells, that lodge in the dermis and epidermis, they release IL-2, gamma-interferon and other cytokines, which attract lymphocytes CD8 +, which induce cell transient amplification. The resulting explosion of hyperproliferative activity is the basis of guttate lesions. The epidermis hyperproliferative activity also increases the expression of keratins, such as keratin 14. The cycle can be perpetuated and exacerbated by T cells, that are specifically sensitized to the M protein of Streptococcus that shows a strong homology with the keratin 14 of the skin.

There is other evidence of the immunological basis of psoriasis:

a. bone marrow transplants in patients with psoriasis cause psoriasis spent recipients, while bone marrow from normal individuals may induce a remission of the disease;

b. similar results were obtained experimentally in mice with severe combined immunodeficiency;

c. all substances effective in the treatment of psoriasis, act on T cells (cyclosporine, rapamycin, corticosteroids, retinoids, vitamin D and analogues, methotrexate).

Treatment outcomes of tonsillectomy were studied in 13 italian patients with psoriasis- 6 males and 5 females aged 9 to 46 years - followed up 2 to 5 years after tonsillectomy. There were 8 cases of guttate psoriasis and 5 cases of chronic plaque psoriasis. The PASI score improved for at least 50% for the entire follow-up period in two patients and in a short period (not inferior to 6 months) in 7 patients. A little improvement of PASI score (30%) was observed for 18 months in 1 patient. No change was found in the remaining 3 during follow-up period. Out of 9, whose skin lesions have improved, 4 were females and had a history of tonsillitis making skin lesions worse.

Light microscopy and SEM findings showed minimal differences between the control and both psoriatic subgroup A and B. At light microscopy examination, clear follicular expansion and irregularity as well as evident infiltration of lymphoid cells in the tonsillar crypt epithelium, along with irregularity of the epithelial wavy basal membrane and epithelial basal profile were noted in two cases from psoriatic subgroup B.

This preliminary report needs further investigation on a more large casuistry for conclusions validation. The paper is not intended to promote the tonsillectomy for the treatment of psoriasis, but try to contribute to the now confirmed conviction of the international literature on the relationship between psoriasis and streptococcal infection.

However, despite Cochrane review[56] conclusions, numerous reports indicate the improving role of tonsillectomy in some cases of psoriasis. The challenge of future research is the understanding of what kind of patients are susceptible to this improvement, in order to customize the use of the surgical treatment of tonsillectomy for patients with psoriasis and to better define the relationship between this disease and streptococcal infection.

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