Journal of Pediatric Sciences

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Journal of Pediatric Sciences 2014;6:e211

How to cite this article:

Pac M, Olczak-Kowalczyk D, Wolska-Kuśnierz B, Piątosa B, Górska R, Bernatowska E . Recurrent Oral Inflammations in Autoimmune Lymphoproliferative Syndrome. Journal of Pediatric Sciences. 2014;6:e211

ORIGINAL ARTICLE

Recurrent Oral Inflammations in Autoimmune Lymphoproliferative Syndrome

Małgorzata Pac[1], Dorota Olczak-Kowalczyk[2], Beata Wolska-Kuśnierz[1], Barbara Piątosa[3], Renata Górska[4], Ewa Bernatowska[1]

[1]Department of Immunology, The Children's Memorial Health Institute, [2]Department of Pediatric Dentistry, Medical University of Warsaw, [3]Histocompatibility Laboratory, The Children's Memorial Health Institute, [4]Department of Periodontology and Oral Medicine, Medical University of Warsaw, Warsaw, Poland

Abstract:

Background and aim: *Autoimmune lymphoproliferative syndrome (ALPS) is a disorder of abnormal lymphocyte survival caused by dysregulation of the Fas apoptotic pathway. In ALPS defective lymphocyte apoptosis manifests as a chronic, nonmalignant lymphadenopathy and/or splenomegaly/hepatosplenomegaly, expansion of double negative T cell (DNTC) – CD4-CD8-TCRαβ+ T cells, autoimmune cytopenias and other autoimmune diseases. Patients demonstrate oral lesions which have not yet been reported in the literature. The aim of the study was to present the oral status of children with ALPS, associated mainly with haematologic and immunologic disorders.* ***Material and methods:*** *Among almost 1500 patients with primary immune deficiency diagnosed between 1980 and 2012 at the Department of Immunology, Children's Memorial Hospital, Warsaw (Poland) 7 cases of ALPS were identified according to ALPS diagnostic criteria. Routine immunological parameters were evaluated (serum immunoglobulin levels, immunophenotyping of peripheral lymphocytes, DNT cells, proliferative response to mitogens), vitamin B12 level, haematological and biochemical laboratory tests. Clinical course was retrieved retrospectively from medical records and evaluated during control visits. All patients were offered dental evaluation and treatment. Clinical examinations included the status of marginal gingiva, oral mucosa (the presence and type of lesions) and presence of caries.* ***Results and conclusions:*** *Almost all patients presented with leukopenia and granulocytopenia during control visits. Unsatisfactory oral hygiene status, carious cavities and gingivitis were found in all patients. In six subjects oral ulcers were also noticed. In two of them gingivitis was assessed as severe (with redness, swelling and spontaneous gingival bleeding), in other - as mild. An association between hematological and immune disorders and the health status of the oral mucosa and gingivae was observed in all but one patient. Findings included pale oral mucosa, a smooth tongue, recurrent mucosal ulcers, and gingivitis with bleeding. Their onset was accompanied by deterioration in the patients' general health condition and the presence of local causative factors. Recurrent oral inflammation/aphtae can be the first symptom of ALPS and should be taken into account in differential diagnosis by paediatrician or general practitioner. It indicates strong need for cooperation between the dentists and immunologists and haematologists.*

Keywords: *autoimmune lymphoproliferative syndrome, neutropenia, gingivitis, oral ulcers, dental caries*

Corresponding author: *Małgorzata Pac, Department of Immunology, Children's Memorial Health Institute, Warsaw, Phone: +48 22 815 73 78, fax: +48 22 815 18 39, e-mail: malgorzata.pac@wp.pl*

Introduction

Autoimmune lymphoproliferative syndrome (ALPS) is a disorder of abnormal lymphocyte survival caused by dysregulation of the Fas apoptotic pathway (programmed cell death). In the immune system, antigen-induced lymphocyte apoptosis maintains immune homeostasis by

Table 1. **Revised classification of ALPS and ALPS-related disorders (report from 2009 NIH International Workshop, Oliveira JB, Blessing JJ et al, Blood, 2010)**

Previous nomenclature	Revised nomenclature	Gene	Definition
APLS type 0	ALPS-FAS	FAS	Patients fulfill ALPS criteria and have germline homozygous mutation in FAS
ALPS type Ia	ALPS-FAS	FAS	Patients fulfill ALPS criteria and have germline heterozygous mutation in FAS
ALPS type Im	ALPS-sFAS	FAS	Patients fulfill ALPS criteria and have somatic mutation in FAS
ALPS Ib	ALPS-FASLG	FASLG	Patients fulfill ALPS criteria and have germline mutations in FAS ligand
ALPS type IIa	ALPS-CASP10	CASP10	Patients fulfill ALPS criteria and have germline mutation in caspase 10
AL PS type III	ALPS-U	Unknown	Patients meet ALPS criteria but genetic defect is not determined
ALPS type IIb	CEDS	CASP8	Patients present with lymphadenopathy and/or splenomegaly, marginal DNT elevation, recurrent infections and germline mutations in caspase 8
ALPS type IV	RALD	NRAS	Patients present with autoimmunity, lymphadenopathy and/or splenomegaly, elevated or normal DNT's and somatic mutations in NRAS
DALD	DALD	Unknown	Patients present with autoimmunity, lymphadenopathy and/or splenomegaly, normal DNT's and defective in vitro FAS-mediated apoptosis
XLP1	XLP1	SH2D1A	Patients present with fulminant Epstein-Barr virus infection, hypogammaglobulinemia and lymphoma

limiting lymphocyte accumulation and minimizing reactions against self-antigens.

Defective apoptosis can lead to uncontrolled lymphoproliferation, autoimmunity, and malignancy. The pathognomonic laboratory finding is accumulation of a mature, polyclonal population of TCRαβ+CD4-CD8-Tcells (double-negative T cells – DNTC). The other plasma biomarkers routinely assayed in diagnostic procedures include sFASL (soluble FAS ligand), interleukin-10 (IL-10), interleukin-18 (IL-18), and vitamin B12.

In the majority of cases, the disease becomes overt in early childhood, usually before 5 years of age. ALPS occurs in both sexes, many ethnic groups, although its incidence has not been determined yet. Some reports show that boys are more frequently affected [1].

Clinically, ALPS is manifested by several pathologies of different frequency. According to Blessing, all patients develop splenomegaly; most of them lymphadenopathy and half of them hepatomegaly. [1-3]. Many patients show autoimmune features, mainly cytopenias [1-7]. Autoimmune haemolytic anaemia and thrombocytopenia are predominant. Neutropenia affects about 1/3 of patients and is manifested in recurrent oral ulcers and stomatitis. An increased risk of both Hodgkin and non-Hodgkin lymphomas, frequently initiated by Epstein-Barr virus infection, has also been reported [1-4].

Other clinical symptoms are of less frequency, including glomerulonephritis, autoimmune hepatitis, vasculitis, CNS manifestations (i.e. headaches, seizures), and arthritis [8].

The molecular basis of ALPS was described in

Table 2. Revised diagnostic criteria for ALPS (report from 2009 NIH International Workshop, Oliveira JB, Blessing JJ et al, Blood, 2010)

Required

- Chronic (>6 months), non-malignant, non-infectious lymphadenopathy and/or splenomegaly
- 2. Elevated CD3+TCRαβ+CD4-CD8- DNT cells (equal to or greater than 1.5% of total lymphocytes or 2.5% of CD3+lymphocytes) in the setting of normal or elevated lymphocyte counts

Accessory

Primary

- Defective lymphocyte apoptosis (in 2 separate assays)
- Somatic or germline mutations in FAS, FASLG, or CASP10

Secondary

- Elevated plasma sFAS levels (>200 pg/ml) OR elevated plasma IL-10 levels (>20 pg/ml) OR elevated serum or plasma vitamin B12 levels (>1500 ng/ml) OR elevated plasma IL-18 levels (>500 pg.ml)
- Typical immune-histological findings
- Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) AND elevated IgG levels (polyclonal hypergammaglobulinemia)
- 4. Family history of a non-malignant/non-infectious lymphoproliferation with or without autoimmunity

Definitive diagnosis

Both required plus one primary accessory criteria

Probable diagnosis

Both required plus one secondary accessory criteria

the 1990's and the syndrome was thought to be very rare. Since then great progress has been made in molecular diagnostics of ALPS, resulting in earlier and better treatment. Approximately 70% of patients are affected by mutation in Fas pathway genes. The most common is a germline mutation in the Fas gene, while somatic mutations of the same gene are less common. Other molecular backgrounds of ALPS include mutations in genes encoding Fas-ligand (FasL), caspase-8, and caspase-10. In 2009 the classification of ALPS was modified [9] and both ALPS and ALPS-like syndromes were identified (Table 1).

The criteria of definitive and probable diagnosis were established (Table 2).

Treatment is targeted at controlling lymphocyte proliferation. In patients with autoimmune cytopenias, glucocorticosteroid courses, as well as intravenous infusions of immunoglobulins are usually effective. The management of recurrent episodes of cytopenia involves administration of immunosuppressive drugs (e.g. cyclosporine, methotrexate), anti-CD20 monoclonal antibodies, mycofenolate mofetil or splenectomy [4,10,11,12]. This last one should be considered with care.

Defective apoptosis in ALPS, particularly in patients with autoimmune cytopenias and an impaired function of the immune system, may cause or contribute to oral pathology of infectious, autoimmune and even neoplastic etiology. The implications also determine dental treatment, i.e. the choice of an appropriate therapeutic method and adequate preparation of the patient for dental procedures. Hence, it is important for the dental surgeon to be familiar with the issues concerning autoimmune lymphoproliferative syndrome. However current literature does not provide comprehensive information on oral aspects of the disease.

The aim of this study was to present oral manifestations in patients with ALPS and with or without neutropenia and other haematologic and immunologic disorders.

Material and Methods

Among almost 1500 patients with primary immune deficiency diagnosed between 1980 and 2012 at the Department of Immunology, Children's Memorial Hospital, Warsaw (Poland) 7 cases of ALPS were identified according to ALPS diagnostic criteria. In all patients routine immunological parameters were evaluated, among them serum immunoglobulin levels,

immunophenotyping of peripheral lymphocytes, detection of DNT cells, proliferative response to

mitogens, vitamin B12 level, hematological and biochemical laboratory tests. Phenotypic features (splenomegaly, adenopathy, autoimmunity) were retrieved from medical records and evaluated during physician interviews.

Genetic analyses were done at Necker Hospital, Paris or at Erasmus Medical University, Rotterdam in one and six patients respectively, due to the courtesy of F. Le Deist and J.J. van Dongen.

All patients were offered dental evaluation and treatment. Clinical examinations included the status of marginal gingiva, oral mucosa (the presence and type of lesions) and presence of caries. The oral hygiene status was assessed using the Plaque Index (Pl I). Gingival inflammation was evaluated according to the Gingival Index (GI) [13]. Dental plaque and status of gingivae were examined at four surfaces of six randomly selected teeth [16,12, 24,36,32,44]. The scores from the areas were added and divided by four to give the value of PLI and GI. Gingivitis was assessed according to the following scale: mild (value 0.1-1.0), moderate (value >1.1-2.0), severe (value >2.0). Medical indications, radiological examinations and microbiological tests (mycology, bacteriology, and The Perio-Analyse test, based on the Real Time Polymerase Chain Reaction) were planned.

Results

All seven patients were diagnosed according to old or revised ALPS diagnostic criteria. In six of them the diagnosis of Fas defect was established by molecular analysis. Mutation in Fas and FasL were excluded in one boy with clinical symptoms of ALPS (Table 3).

Clinical symptoms observed in that group of children are presented in table 3. All but one demonstrated lymphadenopathy and/or splenomegaly, and cytopenias. In one boy recurrent aphtosous stomatitis was the main reason of immunological investigations, while marginal cervical lymphadenopathy and splenomegaly as well as one episode of very mild neutropenia were less important and omitted by pediatrician. One of the patients experienced several autoimmune symptoms, including uveitis, nephritis, thrombocytopenia, haemolytic anaemia as well as lymphadenopathy, splenomegaly. In all an elevated DNT cell number and vitamin B12 level were observed.

Almost all patients presented with leukopenia and granulocytopenia during control visits. On readmission, unsatisfactory oral hygiene status, carious cavities and gingivitis were found in all patients. In six subjects oral ulcers were also noticed. In two of them gingivitis was assessed as severe (with redness, swelling and spontaneous gingival bleeding), in other - as mild.

In one of them (pt 6) recurrent aphtous lesions were the leading symptom, while mild gingivitis was observed sporadically. He presented with mild leukopenia, one episode of mild neutropenia, no thrombocytopenia or autoimmune haemolytic anaemia. Mild splenomegaly and mild cervical lympadenopathy were found during physical examination on readmission.

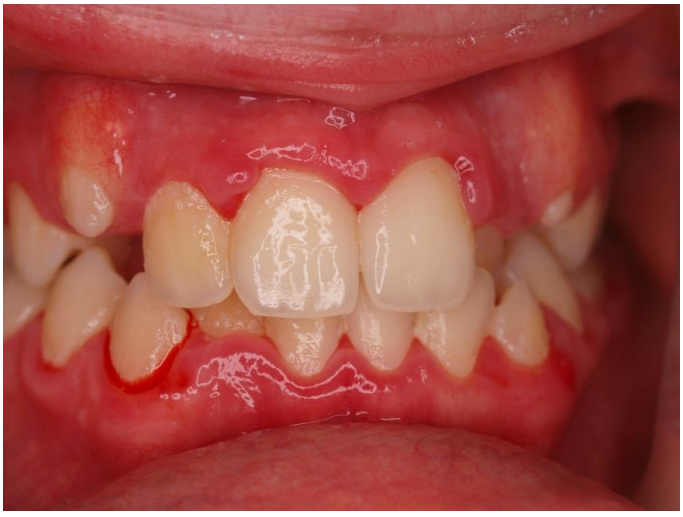

Figure 1. Occlusal abnormalities (crowding, palatal positioning of the left lateral maxillary incisor), gingivitis with redness, swelling and spontaneous bleeding and dental plaque deposits in patient PW with ALPS Ia (courtesy D. Olczak-Kowalczyk, MD PhD).

Table 3. Clinical and laboratory data of patients with ALPS

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Age at diagnosis [years]	6	9	3	12	7	11	6
Sex	M	M	M	M	M	M	M
Onset of symptoms [years, *months]	2	7	5 *	10	13*	3	4
Splenomegaly	Y	Y	Y	Y	Y	Y	Y
Lymphadenopathy	Y	Y	Y	Y	Y	Y	Y
Mucosal ulcers	Y	Y	Y	N	Y	Y	Y
Gingivitis	Y	Y	Y	Y	Y	Y	Y
Uveitis	N	N	N	Y	N	N	N
Nephritis	N	N	N	Y	N	N	N
Thrombocytopenia	Y	Y	Y	Y	Y	N	Y
AIHA	Y	Y	N	Y	Y	N	N
Neutropenia	Y	Y	Y	Y	Y	Y	N
DNTC(CD3+TCRαβ+CD4-CD8-) [% TCRαβ+]	4.1	9	16.6	5.4	11.5	11.1	28
Vit B12 [pg/ml]	nd	>2000	>2000	3380	Nd	1481	4 672
IgG [g/l]	64.0	21.1	24.4	14.6	15.2	19.0	3.24
IgA [g/l]	32.0	9.21	3.07	3.5	1.24	3.18	4.32
IgM [g/l]	0.73	0.76	0.36	0.96	0.18	0.77	0.77
Mutation	*FAS*	*FAS*	*FAS*	*FAS*	No *FAS/FASLG*	*FAS*	*FAS*

In patient 2 with severe gingivitis a crater-like ulcer localised on the right lingual margin was found (Figure 1 and 2).

Streptococcus viridans and Neisseria spp colonies were cultured from sample obtained from the ulcer. We observed occlusal abnormalities, gothic palate, angular cheilitis (coexistent with 103CFU/ml Candida albicans), smoothness and a midline schistoglossia, pallor of the palatal mucosa too. Pantomography revealed initial signs of alveolar bone ridge destruction. The Perio-Analyse test, based on the Real Time Polymerase Chain Reaction (RT-PCR), was positive for Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum, Campylobacter rectus, Eikenella corrodens. The patient was offered instruction on oral hygiene. Topical treatment was performed, with scaling under antibiotic cover, and on five sessions active oxygen was applied into the periodontal pockets and onto the lingual ulceration (using the OzonyTron® device). Despite improvements in oral hygiene a subsequent examination performed six weeks later showed only a minimally decreased severity of gingivitis (no spontaneous bleeding) and an aphthoid erosion (RAS major) in the lower lip mucosa.

In the next patient (nr 5) with severe gingivitis oral examination showed carious cavities at various progression stages in 18 teeth, including nine deciduous teeth with pulp gangrene, very poor oral hygiene and three streptococcal, crater-

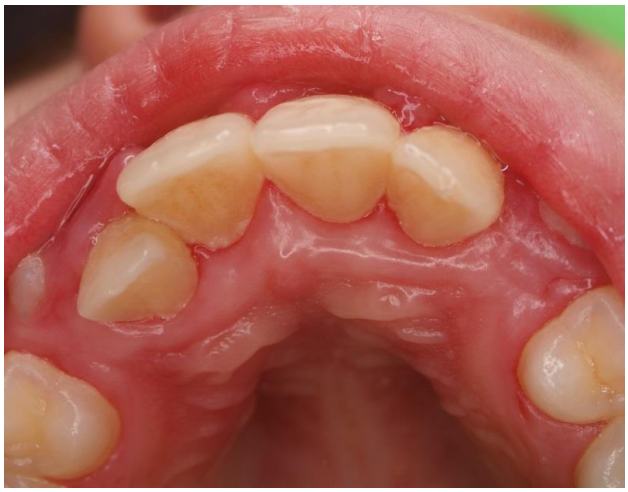

Figure 2. Gingivitis, redness, swelling, spontaneous bleeding, pale palatal mucosa in patient PW with ALPS Ia (courtesy D. Olczak-Kowalczyk,MD PhD).

like ulcers on the left lingual margin, on the left buccal surface at the site of the first permanent mandibular molar, and a large ulcer on the lower lip (Figure 3 a,b,c).

The ulcers had deeply infiltrated the base and were covered by a white fibrous coat. Despite the topical treatment (2% sol. eosini, 0.2% sol. chlorhexidini gluconati, solcoseryl adhesive paste, active oxygen applied with the OzonyTron® device) the lesions had a long healing time (14-21 days) with resultant scars.
The history obtained from the boy's mother showed that the lesions, i.e., painful ulcers in the oral mucosa and angular cheilitis had frequently occurred prior to that episode.

Four patients (1,2,4,5) required steroid therapy due to cytopenias, uveitis and nephritis, generally with good response. Glucocorticoid treatment was administerd several times in two boys (1,2). In the next one (4) long-term therapy with minimal effective dose was continued for months. This patient did not present oral ulcers and aphtae. One patient without neutropenia and no history of steroid therapy presented recurrent aphtosus stomatitis. Among other individuals on steroids two had sporadic episodes of oral ulcers and aphtae, one – recurrent. No obvious correlation between glucocorticoid therapy and aphtae was noticed.

An association between hematological and immune disorders (anaemia, thrombocytopenia, neutropenia) and the health status of the oral mucosa and gingivae was observed in all but one patient. Findings included pale oral mucosa, a smooth tongue, recurrent mucosal ulcers, and gingivitis with bleeding. Their onset was accompanied by deterioration in the patients' general health condition and the presence of local causative factors.

Discussion

Autoimmune lymphoproliferative syndrome is a rare primary immunodeficiency syndrome. Non-specific manifestations affect the diagnostic process and delay the final diagnosis. The patients are frequently referred to hemato-oncologists due to predominant features of lymphatic tissue proliferation such as lymphadenopathy, hepatosplenomegaly, as well as autoimmune cytopenias, either isolated or combined, and other manifestations. The presence of these findings and lack of an unequivocal diagnosis should be considered as an indication to extend the diagnostic protocol of the immune system.

Patients with ALPS visit dental surgeries with a wide spectrum of symptoms, including oral pathologies. The knowledge of the issue helps the dental surgeon initiate an early diagnostic process, and refer the child to a specialist dental clinic.

In all except one of the presented cases, neutropenia was the main factor contributing to the development of oral inflammation. An association between haematological and immune disorders (anaemia, neutropenia, thrombo-cytopenia) and the health status of the oral mucosa and gingivae was observed in vast majority of patients. Other findings included anaemia (pale oral mucosa, a smooth tongue), recurrent mucosal ulcers, and gingivitis with bleeding. Their onset was accompanied by deterioration in the patients' general health condition and the presence of local causative factors. This aspect demonstrates the significance of regular dental care and cooperation between a dental surgeon and an immunologist in the diagnostic and therapeutic management of the patient.

Reports have been published on children with hereditary neutropenia who developed early gingivitis at the developmental stage of the deciduous dentition, which caused a rapidly-progressing destruction of the periodontal tissues and resulted in a loss of teeth, mucosal ulcers, usually of streptococcal etiology, and predisposition to fungal infections [14-18]. These observations are in agreement with the authors' earlier clinical experience and literature reports of oral lesions in children with neutropenia [15-17]. However, the role of local factors contributing to these lesions should not

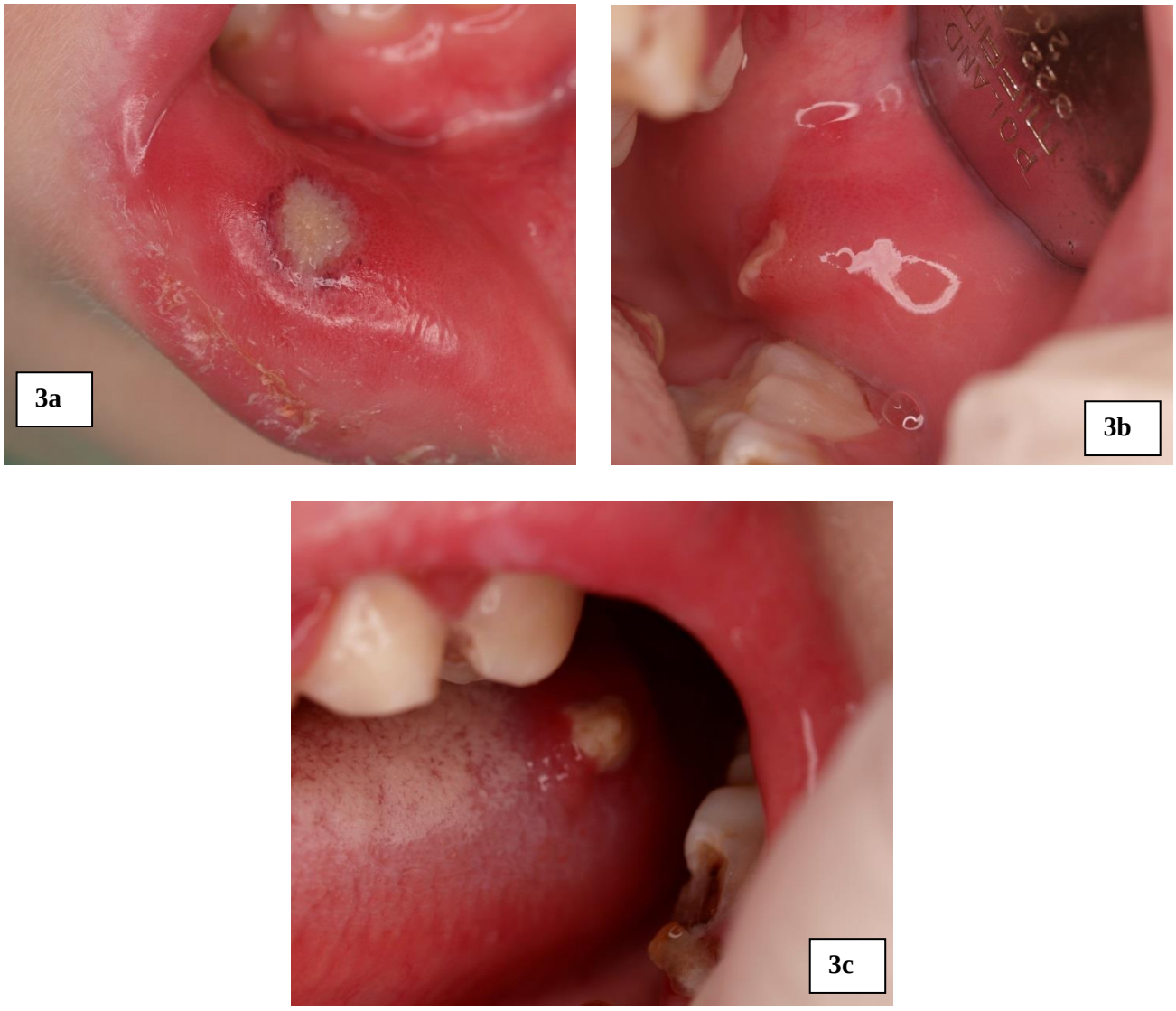

Figure 3. Streptococcal ulcers deeply infiltrating the base: on the right side of the lower lip (a healing stage) (a), of lateral side of the tongue (b), on the left buccal surface in patient MO with ALPS (courtesy D. Olczak-Kowalczyk, MD PhD).

be neglected. In described boys, thick dental plaque deposits were noted. As it is well known, bacteria forming a biofilm on the dental surface are the main etiological factors in caries and periodontal disease. It is a well-known fact that immune disorders related to the innate or adoptive immune response also predispose to recurrent aphthae (RAS) and crater-like ulcers [14]. The latter were found in the boy with ALPS Ia despite a high vitamin B12 concentration, deficiency of which is believed to be one of the RAS etiological factors [19]. Unfortunately, there are no reports presenting the clinical picture of the oral cavity in patients with ALPS. Autoimmune haemolytic anaemia and thrombocytopenia are additional factors predisposing to oral mucosal pathology in children with ALPS. Hemolytic anaemia is manifested by pallor and/or yellowish discoloration of the oral mucosa, particularly in the sublingual area and the soft palate. The yellowish discoloration results from hyperbilirubinemia caused by erythrocytolysis [20]. Thrombocytopenia predisposes to bleeding, mucosal and even submucosal petechiae. In one patient (pt 2) ALPS Ia thrombocytopenia

predisposed to spontaneous bleeding accompanying gingivitis. Bacteriological tests were positive for bacteria of the orange complex according to Socransky (Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatu), which favour development of other anaerobic bacteria, i.e. the red complex, most frequently isolated from patients with periodontitis [21]. Their presence in individuals with neutropenia and occlusal abnormalities compose a very high risk of periodontitis.

Numerous carious cavities and teeth with pulp gangrene in next one indicated no regular dental care. His carious teeth were not treated, despite of the risk of systemic complications. As it is generally known, an increased mucosal permeability accompanying gingivitis or mucosal inflammation, ulceration and erosion carries a high risk of spontaneous dissemination of commensal microorganisms resident in the oral cavity into the blood stream, which may be a severe complication in a child with neutropenia (sepsis, infections in distant organs) [22,23]. Pathogens present in the oral cavity may be aspirated into the child's respiratory tract [22, 24]. Bacterial infections, including Haemophilus influenzae and Mycoplasma pneumoniae, may be present in the oral cavity and are also regarded as factors initiating autoimmunisation [25].

A significant piece of history was supplied by the patient's mother: she admitted that the boy had previously developed frequent ulcerative lesions and angular cheilitis, the presence of which had not been taken into account in the diagnostic process conducted over several years. This fact stresses the need for a regular and thorough assessment of the oral health status, particularly in children with chronic health problems.

Prevention of oral diseases is targeted primarily at elimination of the bacterial factor, early treatment of caries and eradication of inflammatory lesions, and should constitute a constant element of the interdisciplinary care for children with neutropenia.

Regular dental assessment of children with ALPS by a dental surgeon also plays a crucial role in the early diagnosis of neoplastic diseases. The risk of B-cell lymphoma in ALPS Ia is estimated at 10% [26]; 2% of all extranodal lymphomas develop in the oral cavity at such sites as the palate, gingiva, tongue, buccal mucosa, floor of the mouth, and the lips, The lesions are most frequently manifested as palatal and/or maxillary gingival ulcers [27, 28]. Therefore, any non-healing ulcer which increases in size despite a course of treatment constitutes an indication for further diagnostic procedures, primarily a histopathological examination.

Conclusion

A predisposition to chronic or recurrent inflammation in the oral cavity, an increased risk of lymphoma in ALPS, and possible systemic implications of oral pathologies indicate a need for regular dental examination, provision of intensive preventive measures and treatment of oral diseases.

Dental treatment of patients with ALPS, particularly surgical procedures disrupting the tissue continuity, requires full knowledge of the patient's current condition (blood cell count, coagulation parameters, immune status) and the type of the medication administered. Children frequently need to be prepared for dental treatment. Therefore, there is a need for cooperation between the dental surgeon and medical doctor (immunologist, haematologist) treating the underlying disease which is a condition for adequate dental care.

Recurrent oral inflammation and/or aphtosus stomatitis should be taken into account in the diagnostic process by paediatrician or general practitioner as the first symptom of severe disease.

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