Clinical immunology and allergology course
Department of Internal medicine No.2

Diseases of the immune system. Immunodeficiency diseases

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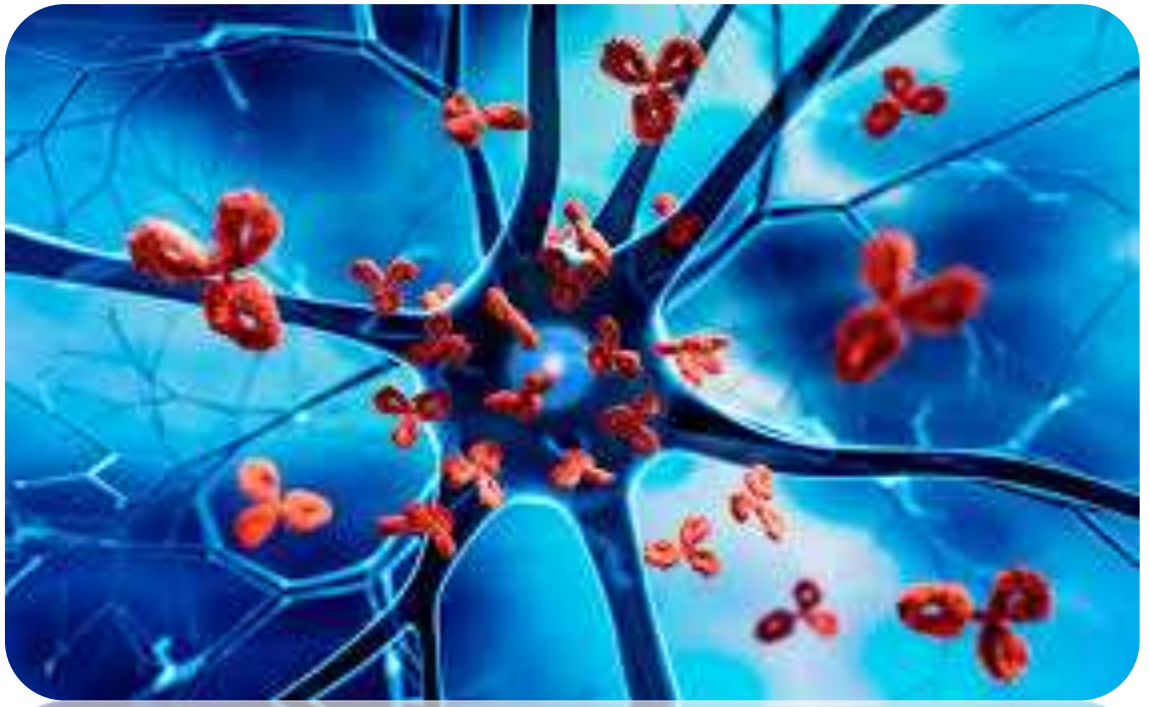


Immunodeficiency disorders are associated with or predispose patients to various complications, including infections, autoimmune disorders, lymphomas and other cancers.

Immunodeficiency can be

- **Primary:** Genetically determined, typically manifesting during infancy or childhood
- **Secondary:** Acquired

Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification

Human inborn errors of immunity (IEI) are caused by monogenic germline mutations resulting in loss or gain of function of the encoded protein. They can be dominant or recessive, autosomal or X-linked, and with complete or incomplete penetrance. They manifest as increased susceptibility to a broad or narrow spectrum of infectious diseases, as well as a growing diversity of autoimmune, autoinflammatory, allergic, and/or malignant phenotypes

- Primary immunodeficiencies are frequently accompanied by autoimmune disease.

- T cell proliferation, and activity can influence the balance between Treg and T helper cells.

- Infections play a role via molecular mimicry, innocent bystander, or epitope spreading.

- Autoimmunity is a “warning sign” for suspecting an immunodeficiency disorder.

Primary immunodeficiencies are genetically determined and can be hereditary;

secondary immunodeficiencies are acquired and much more common

Evaluation of immunodeficiency includes
history, physical examination, and immune function testing.

Testing varies based on the following:

- Whether a primary or secondary immunodeficiency is suspected
- For primary immunodeficiency, which component of the immune system is thought to be deficient

Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee

Table 1 Classification of IEI (IUIS2019)[1]

	Category	Representative diseases
Table 1	Immunodeficiencies affecting cellular and humoral immunity	Severe combined immunodeficiency (SCID)
Table 2	Combined immunodeficiencies with associated or syndromic features	Wiskott-Aldrich syndrome (WAS) Hyper-IgE syndrome (HIE)
Table 3	Predominantly antibody deficiencies	X-linked agammaglobulinemia (XLA) Common variable immunodeficiency (CVID)
Table 4	Diseases of immune dysregulation	Autoimmune polyglandular syndrome (APS) Autoimmune lymphoproliferative syndrome (ALPS)
Table 5	Congenital defects of phagocyte number or function	Chronic granulomatous disease (CGD)
Table 6	Defects in intrinsic and innate immunity	Chronic mucocutaneous candidiasis disease (CMCD)
Table 7	Autoinflammatory disorders	Familial Mediterranean fever (FMF)
Table 8	Complement deficiencies	Hereditary angioedema (HAE)
Table 9	Bone marrow failure	Dyskeratosis congenita
Table 10	Phenocopies of inborn errors of immunity	Ras-associated ALPS like disorder (RALD) Good syndrome

Immunodeficiency typically manifests **as recurrent infections**.

Both **clinical and laboratory findings** are needed for diagnosis

Manifestations of immunodeficiency

Immunodeficiency typically manifests as recurrent infections. However, more likely causes of recurrent infections in children are repeated exposures to infection at day care or school (infants and children may normally have up to 10 respiratory infections/yr), and more likely causes in children and adults are inadequate duration of antibiotic treatment, resistant organisms, and other disorders that predispose to infection (eg, congenital heart defects, allergic rhinitis, ureteral or urethral stenosis, immotile cilia syndrome, asthma, cystic fibrosis, severe dermatitis)

Immunodeficiency should be suspected when recurrent infections are the following:

- Severe
- Complicated
- In multiple locations
- Resistant to treatment
- Caused by unusual organisms
- Present in family members

Initially, infections due to immunodeficiency are typically upper and lower respiratory tract infections (eg, sinusitis, bronchitis, pneumonia) and gastroenteritis, but they may be serious bacterial infections (eg, meningitis, sepsis).

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

10 FOR ADULTS Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known

1. Two or more new ear infections within 1 year.
2. Two or more new sinus infections within 1 year, in the absence of allergy.
3. One pneumonia per year for more than 1 year.
4. Chronic diarrhea with weight loss.
5. Recurrent viral infections (colds, herpes, warts, condyloma).
6. Recurrent need for intravenous antibiotics to clear infections.
7. Recurrent, deep abscesses of the skin or internal organs.
8. Persistent thrush or fungal infection on skin or elsewhere.
9. Infection with normally harmless tuberculosis-like bacteria.
10. A family history of PI.

Secondary Immunodeficiencies

Causes include

- Systemic disorders (eg, diabetes, undernutrition, HIV infection)
- Immunosuppressive treatments (eg, cytotoxic chemotherapy, bone marrow ablation before transplantation, radiation therapy)
- Prolonged serious illness

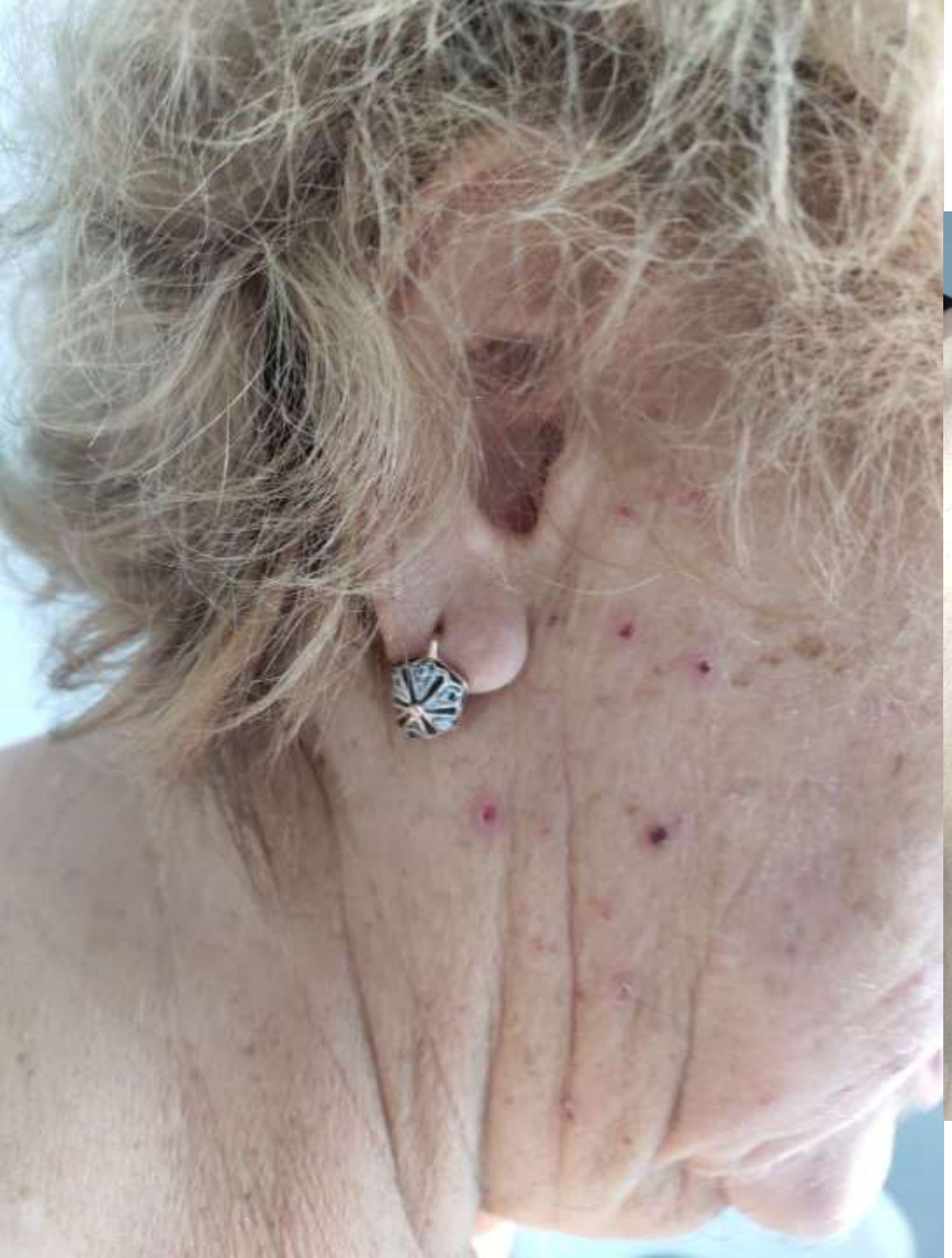
Secondary immunodeficiency also occurs among critically ill, older, or hospitalized patients. Prolonged serious illness may impair immune responses;

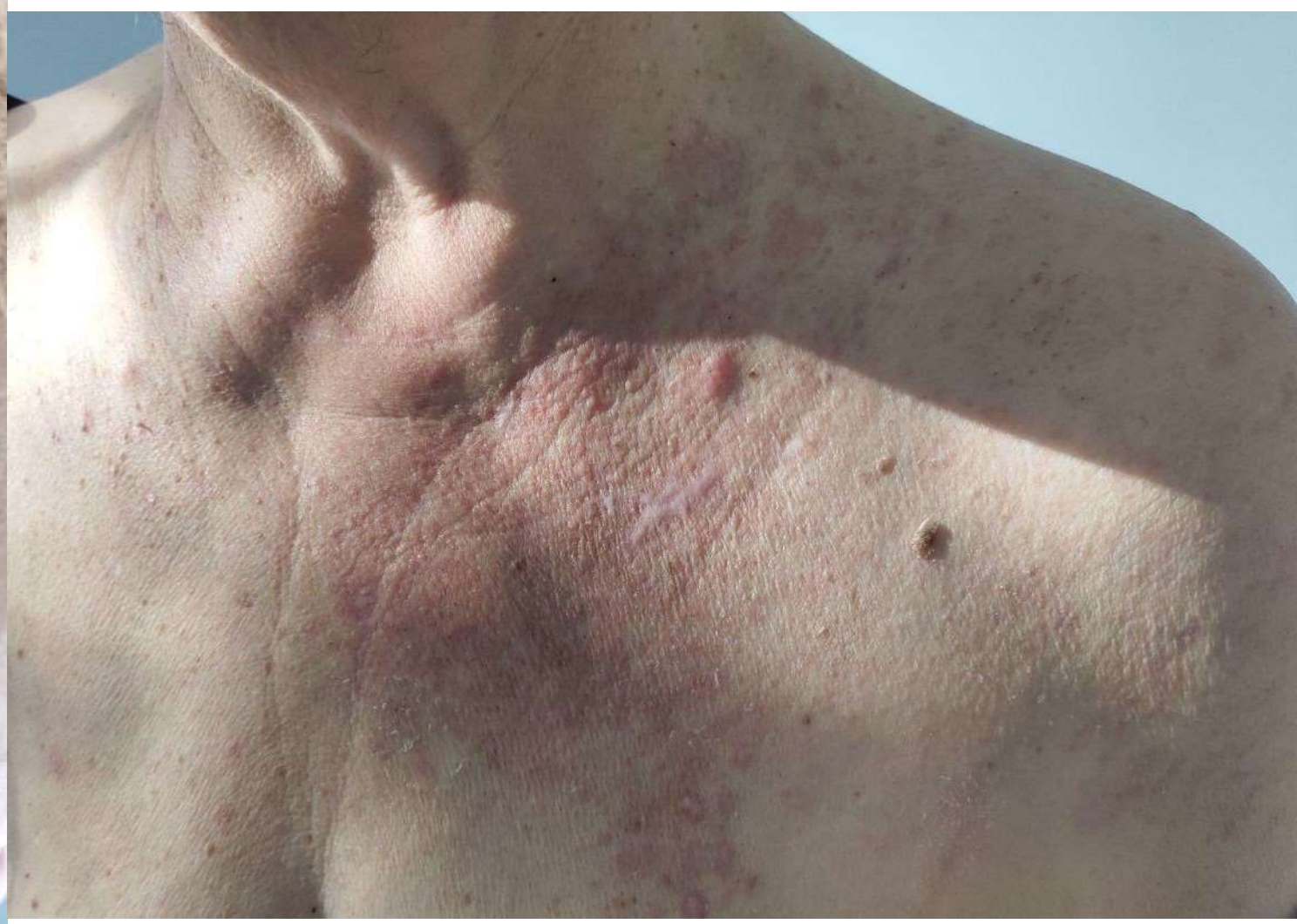
impairment is often reversible if the underlying illness resolves.

Causes of Secondary Immunodeficiency

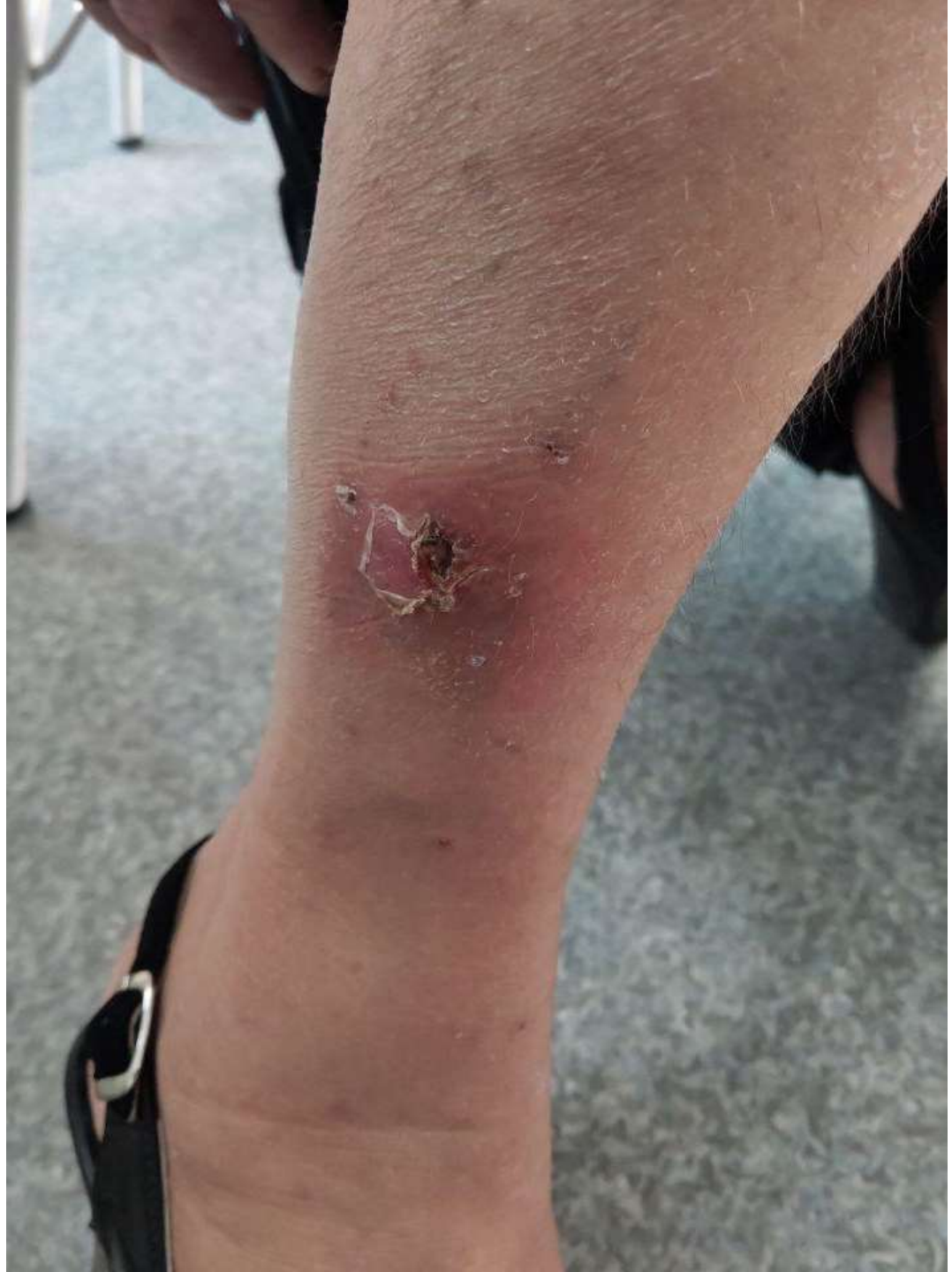
Category	Examples
Endocrine	Diabetes mellitus
GI	Hepatic insufficiency, hepatitis, intestinal lymphangiectasia, protein-losing enteropathy
Hematologic	Aplastic anemia, cancers (eg, chronic lymphocytic leukemia, multiple myeloma, Hodgkin lymphoma), graft-vs-host disease, sickle cell disease, splenectomy
Iatrogenic	Certain drugs, such as chemotherapeutic drugs, immunosuppressants, corticosteroids; radiation therapy; splenectomy

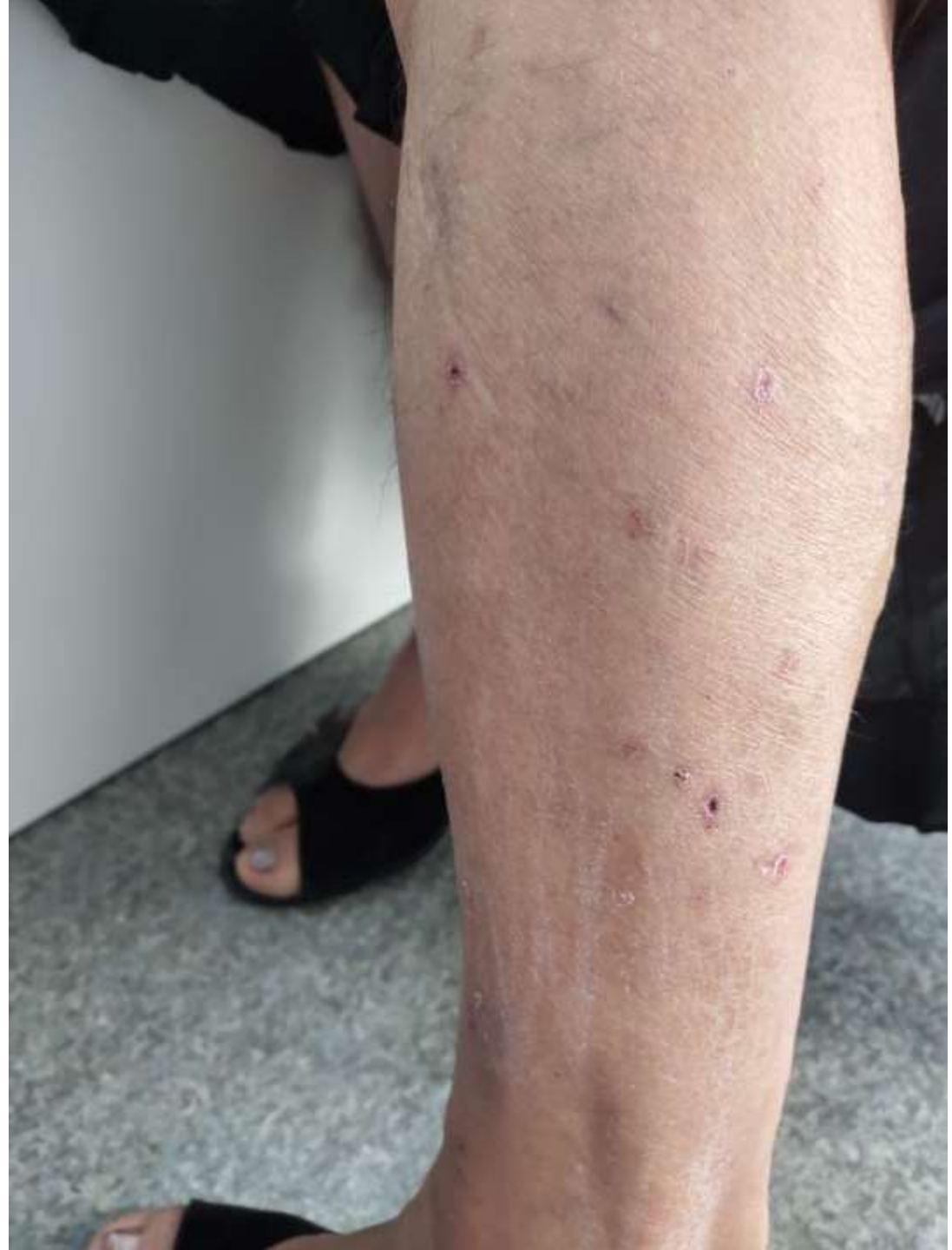
Infectious	Viral infections (eg, cytomegalovirus, Epstein-Barr virus, HIV, measles virus, varicella-zoster virus), bacterial infections, rare bacterial infections with superantigens (antigens that can activate large numbers of T cells, resulting in massive cytokine production, most notably from *Staphylococcus aureus*), mycobacterial infections
Nutritional	Alcoholism, undernutrition
Physiologic	Physiologic immunodeficiency in infants due to immaturity of the immune system, pregnancy
Renal	Nephrotic syndrome, renal insufficiency, uremia
Rheumatologic	SLE
Other	Burns, cancers, chromosomal abnormalities (eg, Down syndrome), congenital asplenia, critical and chronic illness, histiocytosis, sarcoidosis

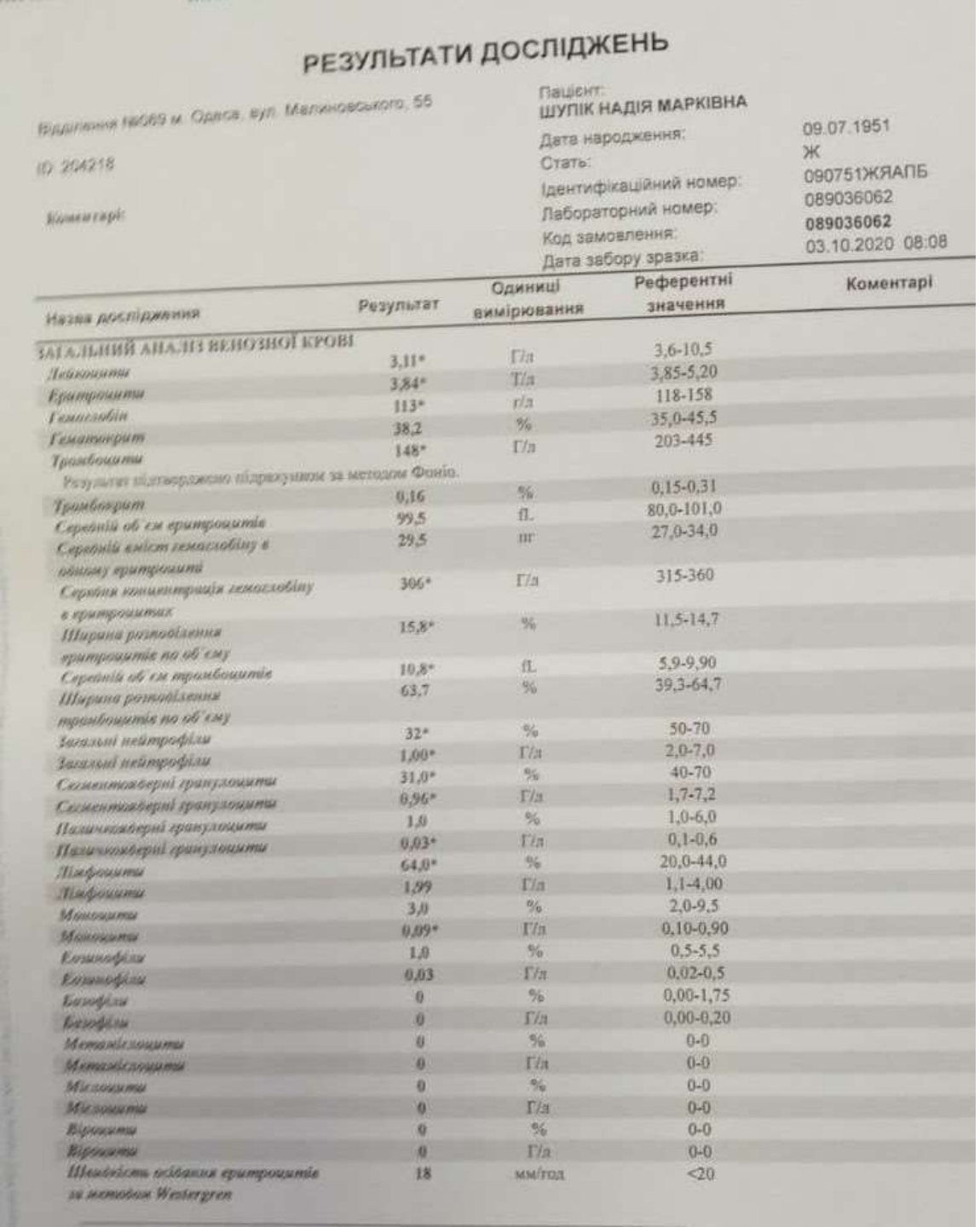




Break till 10:00







РЕЗУЛЬТАТИ ДОСЛІДЖЕНЬ

Відділення №069 м. Одеса, вул. Малиновського, 55

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Коментарі:

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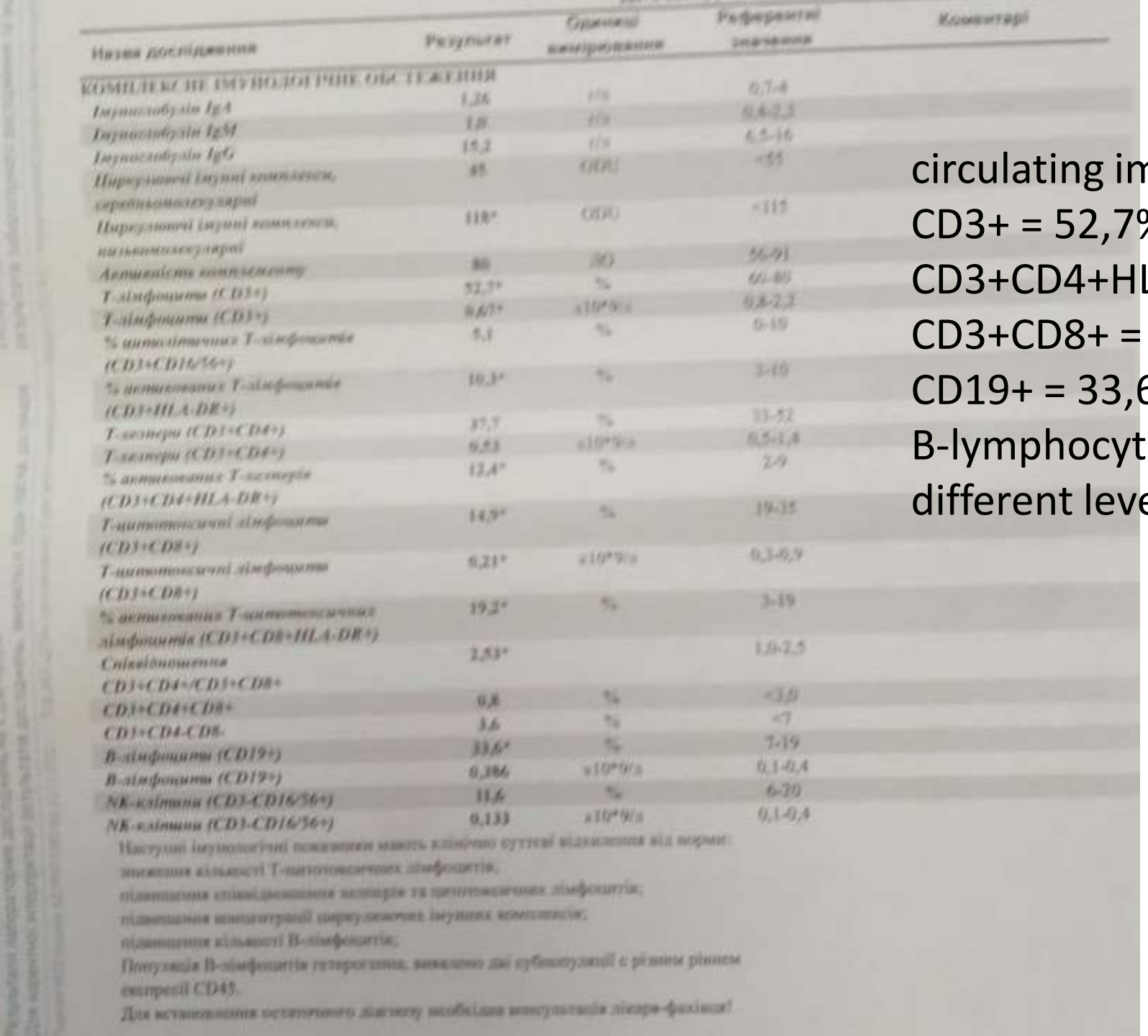
Лабораторний номер: 089036062
Код замовлення: 089036062
Дата забору зразка: 03.10.2020 08:08

Назва дослідження	Результат	Одиниці вимірювання	Референтні значення	Коментарі
ЗАГАЛЬНИЙ АНАЛІЗ ВЕНОЗНОЇ КРОВІ				
Лейкоцити	3,11*	Г/л	3,6-10,5	
Еритроцити	3,84*	Т/л	3,85-5,20	
Гемоглобін	113*	г/л	118-158	
Гематокрит	38,2	%	35,0-45,5	
Тромбоцити	148*	Г/л	203-445	
Результат підтверджено підрахунком за методом Фоніо.				
Тромбокрит	0,16	%	0,15-0,31	
Середній об`єм еритроцитів	99,5	fL	80,0-101,0	
Середній вміст гемоглобіну в одному еритроциті	29,5	пг	27,0-34,0	
Середня концентрація гемоглобіну в еритроцитах	306*	Г/л	315-360	
Ширина розподілення еритроцитів по об`єму	15,8*	%	11,5-14,7	
Середній об`єм тромбоцитів	10,8*	fL	5,9-9,90	
Ширина розподілення тромбоцитів по об`єму	63,7	%	39,3-64,7	
Загальні нейтрофіли	32*	%	50-70	
Загальні нейтрофіли	1,00*	Г/л	2,0-7,0	
Сегментоядерні гранулоцити	31,0*	%	40-70	
Сегментоядерні гранулоцити	0,96*	Г/л	1,7-7,2	
Паличкоядерні гранулоцити	1,0	%	1,0-6,0	
Паличкоядерні гранулоцити	0,03*	Г/л	0,1-0,6	
Лімфоцити	64,0*	%	20,0-44,0	
Лімфоцити	1,99	Г/л	1,1-4,00	
Моноцити	3,0	%	2,0-9,5	
Моноцити	0,09*	Г/л	0,10-0,90	
Еозинофіли	1,0	%	0,5-5,5	
Еозинофіли	0,03	Г/л	0,02-0,5	
Базофіли	0	%	0,00-1,75	
Базофіли	0	Г/л	0,00-0,20	
Метамієлоцити	0	%	0-0	
Метамієлоцити	0	Г/л	0-0	
Мієлоцити	0	%	0-0	
Мієлоцити	0	Г/л	0-0	
Вірогідність	0	%	0-0	
Вірогідність	0	Г/л	0-0	
Швидкість осідання еритроцитів за методом Westergren	18	мм/год	<20	

Wbc = 3,11 G/l (3,6-10,5)
Erythrocytes = 3,84 T/l (3,85-5,20)
Hb = 113 g/l (118-158)
Platelets = 148 Г/l (203-455)
Neutrophils = 32% (50-70), 1 Г/l (2-7)
segmented neutrophils = 31%, 0,96 Г/l (1,7-6,9)
Lymphocytes = 64% (20-44)



Назва дослідження	Результат	Одиниці вимірювання	Референтні значення	Коментарі
КОМПЛЕКСНЕ ІМУНОЛОГІЧНЕ ОБСТЕЖЕННЯ				
Імуноглобулін IgA	1,36	г/л	0,7-4	
Імуноглобулін IgM	1,8	г/л	0,4-2,3	
Імуноглобулін IgG	15,2	г/л	4,5-16	
Циркулюючі імунні комплекси, середньомолекулярні	85	ОДО	<85	
Циркулюючі імунні комплекси, низькомолекулярні	118*	ОДО	<115	
Активність комплементу	80	ЛО	56-91	
Т-лімфоцити (CD3+)	52,7*	%	60-80	
Т-лімфоцити (CD3+)	0,67*	х10*9/л	0,8-2,2	
% цитолітичних Т-лімфоцитів (CD3+CD16/56+)	5,1	%	9-19	
% активованих Т-лімфоцитів (CD3+HLA-DR+)	10,3*	%	3-10	
Т-хелпери (CD3+CD4+)	37,7	%	33-52	
Т-хелпери (CD3+CD4+)	0,53	х10*9/л	0,5-1,4	
% активованих Т-хелперів (CD3+CD4+HLA-DR+)	12,4*	%	2-9	
Т-цитотоксичні лімфоцити (CD3+CD8+)	14,9*	%	19-35	
Т-цитотоксичні лімфоцити (CD3+CD8+)	0,21*	х10*9/л	0,3-0,9	
% активованих Т-цитотоксичних лімфоцитів (CD3+CD8+HLA-DR+)	19,2*	%	3-19	
Співвідношення CD3+CD4+/CD3+CD8+	2,53*		1,0-2,5	
CD3+CD4+CD8+	0,8	%	<3,0	
CD3+CD4-CD8-	3,6	%	<7	
В-лімфоцити (CD19+)	33,6*	%	7-19	
В-лімфоцити (CD19+)	0,386	х10*9/л	0,1-0,4	
NK-клітини (CD3-CD16/56+)	11,6	%	6-20	
NK-клітини (CD3-CD16/56+)	0,133	х10*9/л	0,1-0,4	

Наступні імунологічні показники мають клінічно суттєві відхилення від норми:
зниження кількості Т-цитотоксичних лімфоцитів;
підвищення співвідношення хелпери та цитотоксичних лімфоцитів;
підвищення концентрації циркулюючих імунних комплексів;
підвищення кількості В-лімфоцитів;
Популяція В-лімфоцитів гетерогенна, виявлено дві субпопуляції с різним рівнем експресії CD45.
Для встановлення остаточного діагнозу необхідна консультація лікаря-фахівця!

circulating immune complexes = 118 ODU (<115)
CD3+ = 52,7% (60-80), 0,67*10*9/l (0,8-22)
CD3+CD4+HLA-DR+ = 12,4% (2-9)
CD3+CD8+ = 14,9% (19-35), 0,21*10*9/l (0,3-09)
CD19+ = 33,6% (7-19), 0,4 (0,1-04)
B-lymphocyte population is heterogeneous, different levels of CD45 expression.

Hematology			
Leucocytes	7.38	G/l	3,9 - 10,2
Erythrocytes (RBC)	5.06	T/l	3,9 - 5,2
Hemoglobin	152	g/L	120 - 156
Hematocrit (HCT)	44.7	%	35,5 - 45,5
Thrombocytes (PLT)	262	G/l	166 - 389
Trombokryt (PCT)	0.27	%	0.15 - 0.31
The average volume erythrocytes (MCV)	88.3	fL	80,0 - 99,0
The average hemoglobin in one erythrocyte (MCH)	30.1	pg	27,0 - 33,5
The average concentration of hemoglobin in erythrocytes (MCHC)	340	G/l	315 - 360
Width distribution erythrocytes by volume	12.4	%	11.5 - 14.7

The average volume of thrombocytes (MPV)	10.4*	fL	5.9 - 9.90
Width distribution of thrombocytes in volume (PDW)	49.1	%	39.3 - 64.7
Total Neutrofiles	67	%	50 - 70
Total neutrofiles	4.94	G/l	2.0 - 7.0
Segmented granulocytes (NEU)	65.7	%	40 - 70
Segmented granulocytes (NEU)	4.85	G/l	1,7 - 7,2
Bands granulocytes (BAND)	1.2	%	1.0 - 6.0
Bands granulocytes (BAND)	0.09*	G/l	0.1 - 0.6
Lymphocytes	25.6	%	20,0 - 44,0
Lymphocytes	1.89	G/l	1,1 - 4,5
Monocytes (MONO)	5.3	%	2,0 - 9,5

KDL №405 "Integrated Immunological examination"	1		
Complement activity (CH50)	76	LU	56 - 91
Circulating immune complexes (CIC): mid and lowmolecular			
Circulating immune complexes, mean molecular	29	ODU	< 55
Circulating immune complexes, low molecular	76	ODU	< 115
Subpopulation of lymphocytes			
T-lymphocytes (CD3+)	1.54	x10*9/L	0.8 - 2.2
T-lymphocytes (CD3+)	78.5	%	60 - 80
T-lymphocytes cytolytic, % (CD3+CD16/56+)	5.8	%	0 - 10
T-lymphocytes activated, % (CD3+HLA-DR+)	5.4	%	3 - 10
T-helpers (CD3+CD4+)	53.4*	%	33 - 52

(CD3+HLA-DR+)			
T-helpers (CD3+CD4+)	53.4*	%	33 - 52
T-helpers (CD3+CD4+)	1.05	x10*9/L	0.5 - 1.4
T-cytotoxic lymphocytes activated, % (CD3+CD8+HLA-DR+)	6.1	%	3 - 19
CD3+CD4+CD8+	1.5	%	< 3.0
CD3+CD4-CD8-	4.9	%	< 7
Interrelation CD3+CD4+ / CD3+CD8+	2.29		1.0 - 2.5
B-lymphocytes (CD19+)	0.300	x10*9/L	0.1 - 0.4
B-lymphocytes (CD19+)	15.2	%	7 - 19
NK-cells (CD3-CD16/56+)	0.109	x10*9/L	0.1 - 0.4
NK-cells (CD3-CD16/56+)	5.5*	%	6 - 20
T-helper activated, % (CD3+CD4+HLA-DR+)	3.5	%	2 - 9

Immunodeficiency should also be suspected in infants or young children with **chronic diarrhea** and **failure to thrive**, especially when the diarrhea is caused by unusual viruses (eg, adenovirus) or fungi (eg, Cryptosporidium sp). Other signs include **skin lesions (eg, eczema, warts, abscesses, pyoderma, alopecia), oral or esophageal thrush, oral ulcers, and periodontitis.**

Less common manifestations include severe viral infection with herpes simplex or varicella zoster virus and CNS problems (eg, chronic encephalitis, delayed development, seizure disorder). Frequent use of antibiotics may mask many of the common symptoms and signs. Immunodeficiency should be considered particularly in patients with infections and an autoimmune disorder (eg, hemolytic anemia, thrombocytopenia)

Evaluation

History and physical examination are helpful but must be supplemented by immune function testing.

Prenatal testing is available for many disorders and is indicated if there is a family history of immunodeficiency and the mutation has been identified in family members.

History

Clinicians should determine whether patients have risk factors for infection or a history of symptoms of secondary immunodeficiency disorders and/or risk factors for them. Family history is very important.

Physical examination

Patients with immunodeficiency may or may not appear chronically ill. **Macular rashes, vesicles, pyoderma, eczema, petechiae, alopecia, or telangiectasia may be evident.**

Cervical lymph nodes and **adenoid and tonsillar tissue** are typically very small or absent in X-linked agammaglobulinemia, X-linked hyper-IgM syndrome, severe combined immunodeficiency (SCID), and other T-cell immunodeficiencies despite a history of recurrent infections.

In certain other immunodeficiencies (eg, chronic granulomatous disease), lymph nodes of the head and neck may be enlarged and suppurative.

Tympanic membranes may be scarred or perforated. The nostrils may be crusted, indicating purulent nasal discharge. Chronic cough is common, as are lung crackles, especially in adults with CVID.

The liver and spleen are often enlarged in patients with CVID or chronic granulomatous disease. Muscle mass and fat deposits of the buttocks are decreased.

In infants, skin around the anus may break down because of chronic diarrhea. Neurologic examination may detect delayed developmental milestones or ataxia.

Initial screening tests should include

- CBC with manual differential
- Quantitative immunoglobulin (Ig) measurements
- Antibody titers
- Skin testing for delayed hypersensitivity

Initial and Additional Laboratory Tests for Immunodeficiency

Type	Initial Tests	Additional Tests
Humoral immunity deficiency	IgG, IgM, IgA, and IgE levels Isohemagglutinin titers Antibody response to vaccine antigens (eg, *Haemophilus influenzae* type b, tetanus, diphtheria, conjugated and nonconjugated pneumococcal, and meningococcal antigens)	B-cell phenotyping and count using flow cytometry and monoclonal antibodies to B cells Flow cytometry for CD40 and CD40 ligand Evaluation for mutations in genes that encode BTK and NEMO Sweat test

Cellular immunity deficiency	Absolute lymphocyte count Delayed hypersensitivity skin tests (eg, using *Candida*) HIV testing Chest x-ray for size of thymus in infants only	T-cell phenotyping and count using flow cytometry and monoclonal antibodies to T cells and subsets T-cell proliferative response to mitogens TREC test (a genetic test that identifies infants with abnormal T cells or a low T-cell count due to SCID or other disorders)

Phagocytic cell defects	Phagocytic cell count and morphology	Flow cytometric oxidative burst measurement using dihydrorhodamine 123 (DHR) or nitroblue tetrazolium (NBT) Flow cytometry for CD18 and CD15 Neutrophil chemotaxis

Complement deficiency	C3 level C4 level CH50 activity (for total activity of the classical pathway) and AH50 activity (for total activity of the alternate complement pathways) C1 inhibitor level and function	Specific component assays

Specific and Advanced Laboratory Tests for Immunodeficiency*

Test	Indications	Interpretation
Humoral immunity deficiency		
IgE level measurement	Abscesses	Levels are high in patients with abscesses and pneumatoceles (hyper-IgE syndrome), partial T-cell deficiencies, allergic disorders, or parasitic infections. Levels may be high or low in patients with incomplete B-cell defects or deficiencies. Isolated deficiency is not clinically significant.
B-cell quantification via flow cytometry	Low Ig levels	< 1% B cells suggests X-linked agammaglobulinemia. B cells are absent in Omenn syndrome.

Lymph node biopsy	For some patients with lymphadenopathy, to determine whether germinal centers are normal and to exclude cancer and infection	Interpretation varies by histology.
Genetic testing (genetic sequencing or mutation analysis)†	B cells < 1% (detected by flow cytometry) Suspicion of a disorder with one or more characteristic mutations	Abnormalities in genes suggest or confirm a diagnosis, as in the following: • *BTK*: X-linked agammaglobulinemia • *SAP*‡: X-linked lymphoproliferative syndrome • NEMO: A combined immunodeficiency Results can also provide prognostic information.

T-cell deficiency		
T-cell enumeration using flow cytometry and monoclonal antibodies §	Lymphopenia, suspected SCID or complete DiGeorge syndrome	Interpretation varies by molecular type of SCID.
T-cell proliferation assays to mitogens, antigens, or irradiated allogeneic WBCs	Low percentage of T cells, lymphopenia, suspected SCID or complete DiGeorge syndrome	Low or absent uptake of radioactive thymidine during cell division indicates a T-cell or combined defect.
Detection of antigens (eg, class II MHC molecules) using monoclonal antibodies or serologic HLA typing	Suspected MHC deficiency, absence of MHC stimulation by cells	Absence of class I or class II HLA antigens by serologic HLA typing is diagnostic for MHC antigen deficiency.

RBC adenosine deaminase assay	Severe lymphopenia	Levels are low in a specific form of SCID.
Purine nucleoside phosphorylase assay	Severe persistent lymphopenia	Levels are low in combined immunodeficiency with normal or elevated Ig levels.
T-cell receptor and signal transduction assays	Phenotypically normal T cells that do not proliferate normally in response to mitogen antigen	Interpretation varies by test.
T-cell receptor excision circle (TREC) test	Screening for SCID and other T-cell disorders	Low numbers suggest a defect that disrupts development or maturation of T cells or that causes apoptosis of T cells.

Combined humoral and cellular immunity deficiencies		
Genetic testing	A suspected combined immunodeficiency disorder	Abnormalities in genes suggest or confirm certain disorders; for example, abnormalities in *NEMO* suggest combined immunodeficiency with defects of NF–kappa B regulation, and abnormalities in *IL-2RG* suggest SCID.
Phagocytic cell defects		
Assays for oxidant products (hydrogen peroxide, superoxide) or proteins (CR3 [CD11] adhesive glycoproteins, NADPH oxidase components)	History of staphylococcal abscesses or certain gram-negative or fungal infections (eg, *Serratia marcescens*, aspergillosis)	Abnormalities confirm phagocytic cell defects or deficiencies.
Phosphorylation assays for signal transducer and activator of transcription (STAT), including STAT1 and STAT4	Recurrent mycobacterial infections	This test is the first one done to check for Mendelian susceptibility to mycobacterial disease (MSMD).

Primary Immunodeficiencies

These disorders are genetically determined; they may occur alone or as part of a syndrome. More than 300 of these disorders have been described, and heterogeneity within each disorder may be considerable. The molecular basis for about 80% is known.

Primary immunodeficiencies typically manifest during infancy and childhood as abnormally frequent (recurrent) or unusual infections. About 70% of patients are < 20 yr at onset; because transmission is often X-linked, 60% are male.

Overall incidence of symptomatic disease is about 1/280 people.

Primary immunodeficiencies are classified by the main component of the immune system that is deficient, absent, or defective:

- Humoral immunity
- Cellular immunity
- Combined humoral and cellular immunity
- Phagocytic cells
- Complement proteins

Age when recurrent infections began is important:

- Onset **before age 6 mo** suggests a **T-cell defect** because maternal antibodies are usually protective for the first 6 to 9 mo.
- Onset **between the age of 6 and 12 mo** may suggest **combined B- and T-cell defects or a B-cell defect**, which becomes evident when maternal antibodies are disappearing (at about age 6 mo).
- Onset **much later than 12 mo** usually suggests a **B-cell defect or secondary immunodeficiency.**

In general, the earlier the age at onset in children, the more severe the immunodeficiency.

Often, certain other primary immunodeficiencies (eg, common variable immunodeficiency [CVID]) do not manifest until adulthood.

If results are normal, immunodeficiency (especially Ig deficiency) can be excluded.
If results are abnormal, further tests in specialized laboratories are needed to identify specific deficiencies.
If chronic infections are objectively documented, initial and specific tests may be done simultaneously.
If clinicians suspect that immunodeficiency may be still developing, tests may need to be repeated, with monitoring over time, before a definitive diagnosis is made

CBC can detect abnormalities in one or more cell types (eg, WBCs, platelets) characteristic of specific disorders, as in the following:

- **Neutropenia** (absolute neutrophil count < 1200 cells/µL) may be congenital or cyclic or may occur in aplastic anemia.
- **Lymphopenia** (lymphocytes < 2000/µL at birth, < 4500/µL at age 9 mo, or < 1000/µL in older children or adults) suggests a T-cell disorder because 70% of circulating lymphocytes are T cells.
- **Leukocytosis** that persists between infections may occur in leukocyte adhesion deficiency.
- **Thrombocytopenia** in male infants suggests **Wiskott-Aldrich syndrome.**
- **Anemia** may suggest anemia of chronic disease or autoimmune hemolytic anemia, which may occur in **CVID** and other immunodeficiencies.

However, many abnormalities are transient manifestations of infection, drug use, or other factors; thus, abnormalities should be confirmed and followed.

Peripheral blood smear should be examined for Howell-Jolly bodies (residual fragments of the nucleus in RBCs) and other unusual RBC forms, which suggest primary asplenia or impaired splenic function. Granulocytes may have morphologic abnormalities (eg, giant granules in Chédiak-Higashi syndrome).

Quantitative serum Ig levels are measured. Low serum levels of IgG, IgM, or IgA suggest antibody deficiency, but results must be compared with those of age-matched controls. An IgG level < 200 mg/dL usually indicates significant antibody deficiency, although such levels may occur in protein-losing enteropathies or nephrotic syndrome.

IgM antibodies can be assessed by measuring isohemagglutinin titers (anti-A, anti-B). All patients except infants < 6 mo and people with blood type AB have natural antibodies at a titer of ≥ 1:8 (anti-A) or ≥ 1:4 (anti-B). Antibodies to blood groups A and B and to some bacterial polysaccharides are selectively deficient in certain disorders (eg, Wiskott-Aldrich syndrome, complete IgG2 deficiency).

IgG antibody titers can be assessed in immunized patients by measuring antibody titers before and after administration of vaccine antigens (Haemophilus influenzae type B, tetanus, diphtheria, conjugated or nonconjugated pneumococcal, and meningococcal antigens); a less-than-twofold increase in titer at 2 to 3 wk suggests antibody deficiency regardless of Ig levels. Natural antibodies (eg, antistreptolysin O, heterophil antibodies) may also be measured.

With **skin testing**, most immunocompetent adults, infants, and children react to 0.1 mL of Candida albicans extract (1:100 for infants and 1:1000 for older children and adults) injected intradermally. Positive reactivity, defined as erythema and induration > 5 mm at 24, 48, and 72 h, excludes a T-cell disorder. Lack of response does not confirm immunodeficiency in patients with no previous exposure to Candida.

Chest x-ray may be useful in some infants; an absent thymic shadow suggests a T-cell disorder, especially if the x-ray is obtained before onset of infection or other stresses that may shrink the thymus. Lateral pharyngeal x-ray may show absence of adenoidal tissue.

Additional testing

If clinical findings or initial tests suggest a specific disorder of immune cell or complement function, other tests are indicated.

If patients have recurrent infections and lymphopenia, lymphocyte phenotyping using flow cytometry and monoclonal antibodies to T, B, and natural killer (NK) cells is indicated to check for lymphocyte deficiency.

If cellular immunity deficiency is suspected, the T-cell receptor excision circle (TREC) test can be done to identify infants with low T-cell counts. If tests show that T cells are low in number or absent, in vitro mitogen stimulation studies are done to assess T-cell function. If MHC antigen deficiency is suspected, serologic (not molecular) HLA typing is indicated. Some experts recommend screening all neonates with a TREC test; testing is done routinely in some US states.

If humoral immunity deficiency is suspected, patients may be tested for specific mutations—for example, in the genes that encode for Bruton tyrosine kinase (BTK), CD40 and CD40 ligand, and nuclear factor-kappa-B essential modulator (NEMO). A sweat test is typically done during the evaluation to rule out cystic fibrosis.

If combined cellular and humoral immunity is impaired and SCID is suspected, patients can be tested for certain typical mutations (eg, in the IL-2 receptor gamma [IL-2RG, or IL-2Rγ] gene).

If phagocytic cell defects are suspected, CD15 and CD18 are measured by flow cytometry and neutrophil chemotaxis is tested. A flow cytometric oxidative (respiratory) burst assay (measured by dihydrorhodamine 123 [DHR] or nitroblue tetrazolium [NBT]) can detect whether oxygen radicals are produced during phagocytosis; no production is characteristic of chronic granulomatous disease.

If the type or pattern of infections suggests complement deficiency, the serum dilution required to lyse 50% of antibody-coated RBCs is measured. This test (called CH50) detects complement component deficiencies in the classical complement pathway but does not indicate which component is abnormal. A similar test (AH50) can be done to detect complement deficiencies in the alternative pathway.

Prenatal and neonatal diagnosis

An increasing number of primary immunodeficiency disorders can be diagnosed prenatally using **chorionic villus sampling**, cultured amniotic cells, or fetal blood sampling, but these tests are used only when a mutation in family members has already been identified. X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, ataxia-telangiectasia, X-linked lymphoproliferative syndrome, all forms of SCID (using the TREC test), and all forms of chronic granulomatous disease can be detected.
Sex determination by ultrasonography can be used to exclude **X-linked disorders**

Prognosis

Prognosis depends on the primary immunodeficiency disorder.

Most patients with an Ig or a complement deficiency have a good prognosis with a near-normal life expectancy if they are diagnosed early, are treated appropriately, and have no coexisting chronic disorders (eg, pulmonary disorders such as bronchiectasis).

Other immunodeficient patients (eg, those with a phagocytic cell defect or combined immunodeficiencies, such as Wiskott-Aldrich syndrome or ataxia-telangiectasia) have a guarded prognosis; most require intensive and frequent treatment.

Some immunodeficient patients (eg, those with SCID) die during infancy unless immunity is provided through transplantation. All forms of SCID could be diagnosed at birth if a T-cell receptor excision circle (TREC) test were routinely done in neonates. Suspicion for SCID, a true pediatric emergency, must be high because prompt diagnosis is essential for survival. If SCID is diagnosed before patients reach age 3 mo, transplantation of stem cells from a matched or half-matched (haploidentical) relative is lifesaving in 95%.

Break till 11:30

Treatment

- Avoidance of live vaccines and exposure to infection
- Antibiotics and sometimes surgery
- Replacement of missing immune components

Treatment of immunodeficiency disorders generally involves preventing infection, managing acute infection, and replacing missing immune components when possible

Management of acute infection

After appropriate cultures are obtained, antibiotics that target likely causes should be given promptly. Sometimes surgery (eg, to drain abscesses) is needed.
Usually, self-limited viral infections cause severe persistent disease in immunocompromised patients. Antivirals (eg, oseltamivir, peramivir, or zanamivir for influenza; acyclovir for herpes simplex and varicella-zoster infections; ribavirin for respiratory syncytial virus or parainfluenza 3 infections) may be lifesaving

Replacement of missing immune components

Such replacement helps prevent infection. Therapies used in more than one primary immunodeficiency disorder include the following:

- **IV immune globulin (IVIG)** is effective replacement therapy in most forms of antibody deficiency. The usual dose is 400 mg/kg once/mo; treatment is begun at a low infusion rate. Some patients need higher or more frequent doses. IVIG 800 mg/kg once/mo helps some antibody-deficient patients who do not respond well to conventional doses, particularly those with a chronic lung disorder. High-dose IVIG aims to keep IgG trough levels in the normal range (> 600 mg/dL)

- **Subcutaneous immune globulin** (SCIG) can be given instead of IVIG. SCIG can be given at home, usually by patients themselves. The usual dose is 100 to 150 mg/kg once/wk.

Because SCIG and IVIG differ in bioavailability, the dose of SCIG may need to be adjusted if patients are switched from IVIG. With SCIG, local site reactions are a risk, but SCIG seems to have fewer systemic adverse effects.

- **Hematopoietic stem cell transplantation** using bone marrow, cord blood, or adult peripheral blood stem cells is effective for lethal T-cell and other immunodeficiencies.

Pretransplantation chemotherapy is unnecessary in patients without T cells (eg, those with SCID). However, patients with intact T-cell function or partial T-cell deficiencies (eg, Wiskott-Aldrich syndrome, combined immunodeficiency with inadequate but not absent T-cell function) require pretransplantation chemotherapy to ensure graft acceptance. When a matched sibling donor is unavailable, haploidentical bone marrow from a parent can be used. In such cases, mature T cells that cause graft-vs-host disease must be rigorously depleted from parental marrow before it is given. Umbilical cord blood from an HLA-matched sibling can also be used as a source of stem cells. In some cases, bone marrow or umbilical cord blood from a matched unrelated donor can be used, but after transplantation, immunosuppressants are required to prevent graft-vs-host disease, and their use delays restoration of immunity

Humoral immunity deficiencies

Humoral immunity deficiencies (B-cell defects) that cause antibody deficiencies account for 50 to 60% of primary immunodeficiencies. Serum antibody titers decrease, predisposing to bacterial infections.
The most common B-cell disorders are deficiency **of IgG sub-classes, Selective IgA deficiency.**

Humoral Immunity Deficiencies

Disorder	Inheritance	Gene Affected	Clinical Findings
Common variable immunodeficiency	Variable	*TACI*, *ICOS*, *BAFFR*	Recurrent sinopulmonary infections, autoimmune disorders (eg, immune thrombocytopenia, autoimmune hemolytic anemia), malabsorption, giardiasis, granulomatous interstitial lung disease, nodular lymphoid hyperplasia of GI tract, bronchiectasis, lymphoid interstitial pneumonia, splenomegaly; in 10%, gastric carcinoma and lymphoma Usually diagnosed in patients aged 20–40 yr

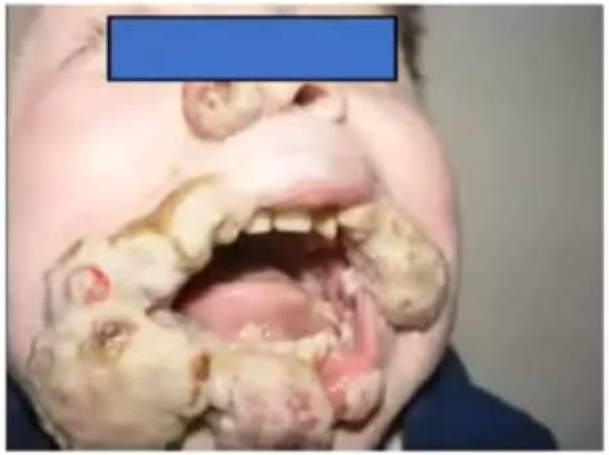
Hyper-IgM syndrome with AID or UNG deficiencies	Autosomal recessive	*AID*, *UNG*	Similar to X-linked hyper-IgM syndrome but with lymphoid hyperplasia No leukopenia
Hyper-IgM syndrome with CD40 deficiency	Autosomal recessive	*CD40*	Similar to X-linked hyper-IgM syndrome Lymphoid hypoplasia, neutropenia
Hyper-IgM syndrome with CD40 ligand deficiency	X-linked	CD40 ligand (CD40L)	Similar to X-linked agammaglobulinemia (eg, recurrent pyogenic bacterial sinopulmonary infections) but greater frequency of *Pneumocystis jirovecii* pneumonia, cryptosporidiosis, severe neutropenia, and lymphoid hypoplasia

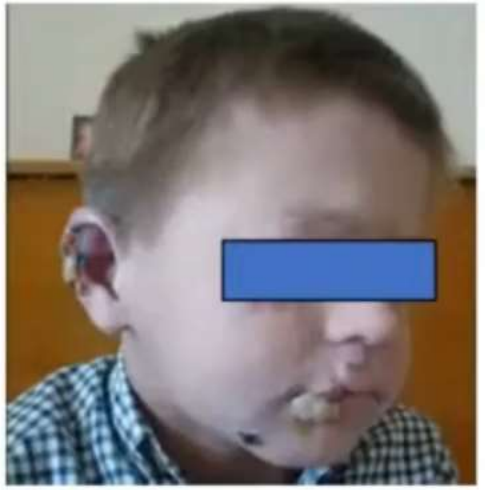
Selective antibody deficiency with normal immunoglobulins	Unknown	—	Recurrent sinopulmonary infections Sometimes atopic manifestations (eg, atopic dermatitis, asthma, chronic rhinitis) Can occur in mild, moderate, severe, and memory phenotypes
Selective IgA deficiency	Unknown	In some cases, *TACI*	Most often asymptomatic Recurrent sinopulmonary infections, diarrhea, allergies (including anaphylactic transfusion reactions [rare]), autoimmune disorders (eg, celiac disease, inflammatory bowel disease, SLE, chronic active hepatitis)

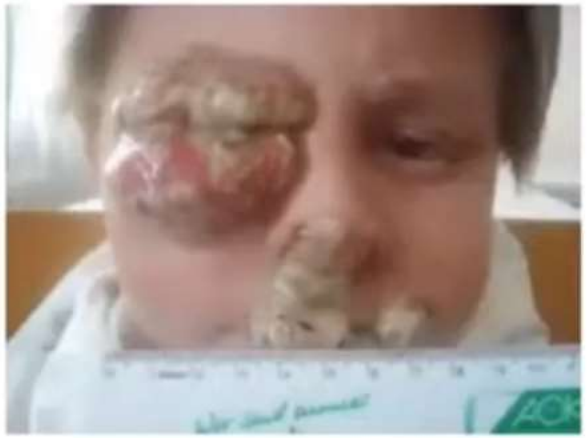
Transient hypogammaglobulinemia of infancy	Unknown	—	Usually asymptomatic Sometimes recurrent sinopulmonary or GI infections, candidiasis, meningitis
X-linked agammaglobulinemia	X-linked	*BTK*	Recurrent sinopulmonary and skin infections during infancy, transient neutropenia, lymphoid hypoplasia Persistent CNS infections resulting from live-attenuated oral polio vaccine, echoviruses, or coxsackieviruses Increased risk of infectious arthritis, bronchiectasis, and certain cancers

Hyper-IgE syndrome	Autosomal dominant or recessive	*STAT3* (dominant) *TYK2*, *DOCK8* (recessive)	Sinopulmonary infections; staphylococcal abscesses of skin, lungs, joints, and viscera; pulmonary pneumatoceles; pruritic dermatitis; coarse facial features; delayed shedding of baby teeth; osteopenia; recurrent fractures; tissue and blood eosinophilia
MHC antigen deficiencies	Autosomal recessive	Various including, *RFX*: RFXANK, RFX5, and RFXAP	Common and opportunistic infections

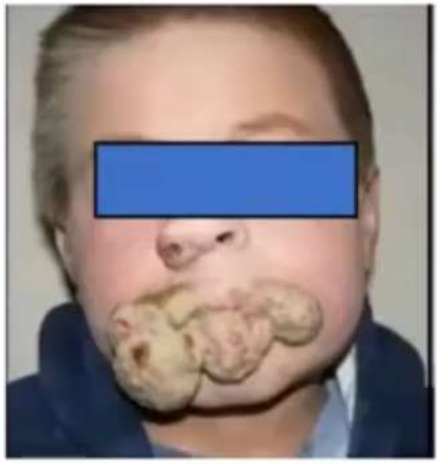
Клітинний імунодефіцит, який потребує для конкретизації генетичного обстеження. Приклад: Іван Л., 22.07.2001 р.н., лікуючі доктори Л.Костюченко, Я.Романишин







Рецедивуючий шкірний аспергільоз



HyperIgE syndrome (DOCK8 deficiency),

велика делеція DOCK8-гену встановлена в університеті Мюнхену

IgE (IU/ml) 25 700

Cellular immunity deficiencies

Cellular immunity deficiencies (T-cell defects) account for about 5 to 10% of primary immunodeficiencies and predispose to infection by viruses, Pneumocystis jirovecii, fungi, other opportunistic organisms, and many common pathogens.

T-cell disorders also cause Ig deficiencies because the B- and T-cell immune systems are interdependent.

The most common T-cell disorders are

- DiGeorge syndrome
- Zeta-associated protein 70 (ZAP-70) deficiency
- X-linked lymphoproliferative syndrome
- Chronic mucocutaneous candidiasis

Primary natural killer cell defects, which are very rare, may predispose to viral infections and tumors. Secondary natural killer cell defects can occur in patients who have various other primary or secondary immunodeficiencies.

Cellular Immunity Deficiencies

Disorder	Inheritance	Gene Affected	Clinical Findings
Chronic mucocutaneous candidiasis	Autosomal dominant or recessive	*STAT1* (dominant) *AIRE* (recessive)	Persistent or recurrent candidal infections, onychomycosis, autosomal recessive autoimmune polyendocrinopathy–candidosis-ectodermal dystrophy (with hypoparathyroidism and adrenal insufficiency)
DiGeorge syndrome	Autosomal	Genes at chromosomal region 22q11.2 Genes at chromosome 10p13	Characteristic facial appearance with low-set ears, a congenital heart disorder (eg, aortic arch abnormalities), thymic hypoplasia or aplasia, hypoparathyroidism with hypocalcemic tetany, recurrent infections, developmental delay
X-linked lymphoproliferative syndrome	X-linked	*SH2D1A* (type 1) *XIAP* (type 2)	Asymptomatic until onset of Epstein-Barr virus infection, then fulminant or fatal infectious mononucleosis with liver failure, B-cell lymphomas, splenomegaly, aplastic anemia
Zeta-associated protein 70 (ZAP-70) deficiency	Autosomal recessive	*ZAP-70*	Common and opportunistic infections No CD8 cells

Combined humoral and cellular immunity deficiencies (B- and T-cell defects) account for about 20% of primary immunodeficiencies

The most important form is Severe combined immunodeficiency (SCID)

Severe combined immunodeficiency is characterized by low to absent T cells and a low, high, or normal number of B cells and natural killer cells. Most infants develop opportunistic infections within the first 3 months of life. Diagnosis is by detecting lymphopenia, absence or a very low number of T cells, and impaired lymphocyte proliferative responses to mitogens. Patients must be kept in a protected environment; de**fi**nitive treatment is hematopoietic stem cell transplantation.

Severe combined immunodeficiency (SCID) is a primary immunodeficiency disorder that involves combined humoral and cellular immunity deficiencies. It is caused by mutations in any one of many different genes (eg, for autosomal recessive forms, Janus kinase 3 [JAK3], protein tyrosine phosphatase, receptor type, C [PTPRC, or CD45], recombination activating genes 1 [RAG1] and 2 [RAG2]). There are various forms of SCID that are autosomal recessive defects, so for the infant to be affected with SCID, the same gene must be mutated on both chromosomes

Symptoms and Signs

By age 6 months, most infants with SCID develop candidiasis, persistent viral infections, Pneumocystis jirovecii pneumonia, and diarrhea, leading to failure to thrive. Some have graft-vs-host disease due to maternal lymphocytes or blood transfusions. Other infants present at age 6 to 12 months. Patients with **Omenn syndrome** may develop exfoliative dermatitis, erythroderma, desquamation, alopecia, chronic diarrhea, failure to thrive, lymphadenopathy, eosinophilia, hepatosplenomegaly, and elevated serum IgE levels. ***ADA deficiency*** may cause bone abnormalities. In all forms, the **thymus is extremely small**, and lymphoid tissue may be decreased or absent.

All forms of SCID are fatal during infancy unless they are diagnosed and treated early

Diagnosis

- Routine neonatal screening using the T-cell receptor excision circle (TREC) test
- History of persistent infections
- White blood cell (WBC) count
- Mitogen and vaccine antigen stimulation assays

The disorder is diagnosed in patients with the following:

- Lymphopenia
- A low number of or no T cells
- Absent lymphocyte proliferative responses to mitogens

Treatment

- Rev**e**rse isolation
- Supportive care using immune globulin replacement therapy, antibiotics, and antifungals
- Hematopoietic stem cell transplantation
- Enzyme replacement for ADA deficiency
- Gene therapy for ADA-deficient SCID

Combined Humoral and Cellular Immunity Deficiencies

Disorder	Inheritance	Gene Affected	Clinical Findings
Ataxia-telangiectasia	Autosomal recessive	*ATM*	Ataxia, telangiectasias, recurrent sinopulmonary infections, endocrine abnormalities (eg, gonadal dysgenesis, testicular atrophy, diabetes mellitus), increased risk of cancer
Cartilage-hair hypoplasia	Autosomal recessive	*RMRP*	Short-limbed dwarfism, common and opportunistic infections
Combined immunodeficiency with inadequate but not absent T-cell function and normal or elevated immunoglobulins	Autosomal recessive or X-linked	*NEMO*	Common and opportunistic infections, lymphopenia, lymphadenopathy, hepatosplenomegaly, skin lesions resembling those of Langerhans cell histiocytosis in some patients

Severe combined immunodeficiency	Autosomal recessive or X-linked	*JAK3*, PTPRC (*CD45*), *RAG1*, *RAG2* (autosomal recessive) *IL-2RG*(X-linked)	Oral candidiasis, *Pneumocystis jirovecii* pneumonia, diarrhea before 6 mo, failure to thrive, graft vs host disease, absent thymic shadow, lymphopenia, bone abnormalities (in ADA deficiency), exfoliative dermatitis as part of Omenn syndrome*
Wiskott-Aldrich syndrome	X-linked recessive	*WASP*	Typically, pyogenic and opportunistic infections, eczema, thrombocytopenia Possibly GI bleeding (eg, bloody diarrhea), recurrent respiratory infections, cancer (in 10% of patients > 10 yr), varicella-zoster virus infection, herpesvirus infection

Phagocytic cell defects

Phagocytic cell defects account for 10 to 15% of primary immunodeficiencies; the ability of phagocytic cells (eg, monocytes, macrophages, granulocytes such as neutrophils and eosinophils) to kill pathogens is impaired (see table Phagocytic Cell Defects). Cutaneous staphylococcal and gram-negative infections are characteristic.

The most common (although still rare) phagocytic cell defects are

- Chronic granulomatous disease
- Leukocyte adhesion deficiency (types 1 and 2)
- Cyclic neutropenia
- Chédiak-Higashi syndrome

Phagocytic Cell Defects

Disorder	Inheritance	Gene Affected	Clinical Findings
Chédiak-Higashi syndrome	Autosomal recessive	*LYST* (CHS1)	Oculocutaneous albinism, recurrent infections, fever, jaundice, hepatosplenomegaly, lymphadenopathy, neuropathy, pancytopenia, bleeding diathesis
Chronic granulomatous disease	X-linked or autosomal recessive	gp91phox (*CYBB*; X-linked) p22phox, p47phox, p67phox (autosomal recessive)	Granulomatous lesions in the lungs, liver, lymph nodes, and GI and GU tract (causing obstruction); lymphadenitis; hepatosplenomegaly; skin, lymph node, lung, liver, and perianal abscesses; osteomyelitis; pneumonia; staphylococcal, gram-negative, and aspergillus infections

Leukocyte adhesion deficiency	Autosomal recessive	*ITGB2* gene, encoding CD18 of beta-2 integrins (type 1) GDP-fucose transporter gene (type 2)	Soft-tissue infections, periodontitis, poor wound healing, delayed umbilical cord detachment, leukocytosis, no formation of pus Developmental delay (type 2)
Mendelian susceptibility to mycobacterial disease (MSMD)	Autosomal dominant or recessive	Defects in genes encoding the IFN-gamma receptor, IL-12, or the IL-12 receptor	Mycobacterial infections Varying clinical severity based on genetic defect
Cyclic neutropenia	Autosomal dominant	*ELA2*	Pyogenic bacterial infections during recurrent episodes of neutropenia (eg, every 14 to 35 days)

Complement deficiencies

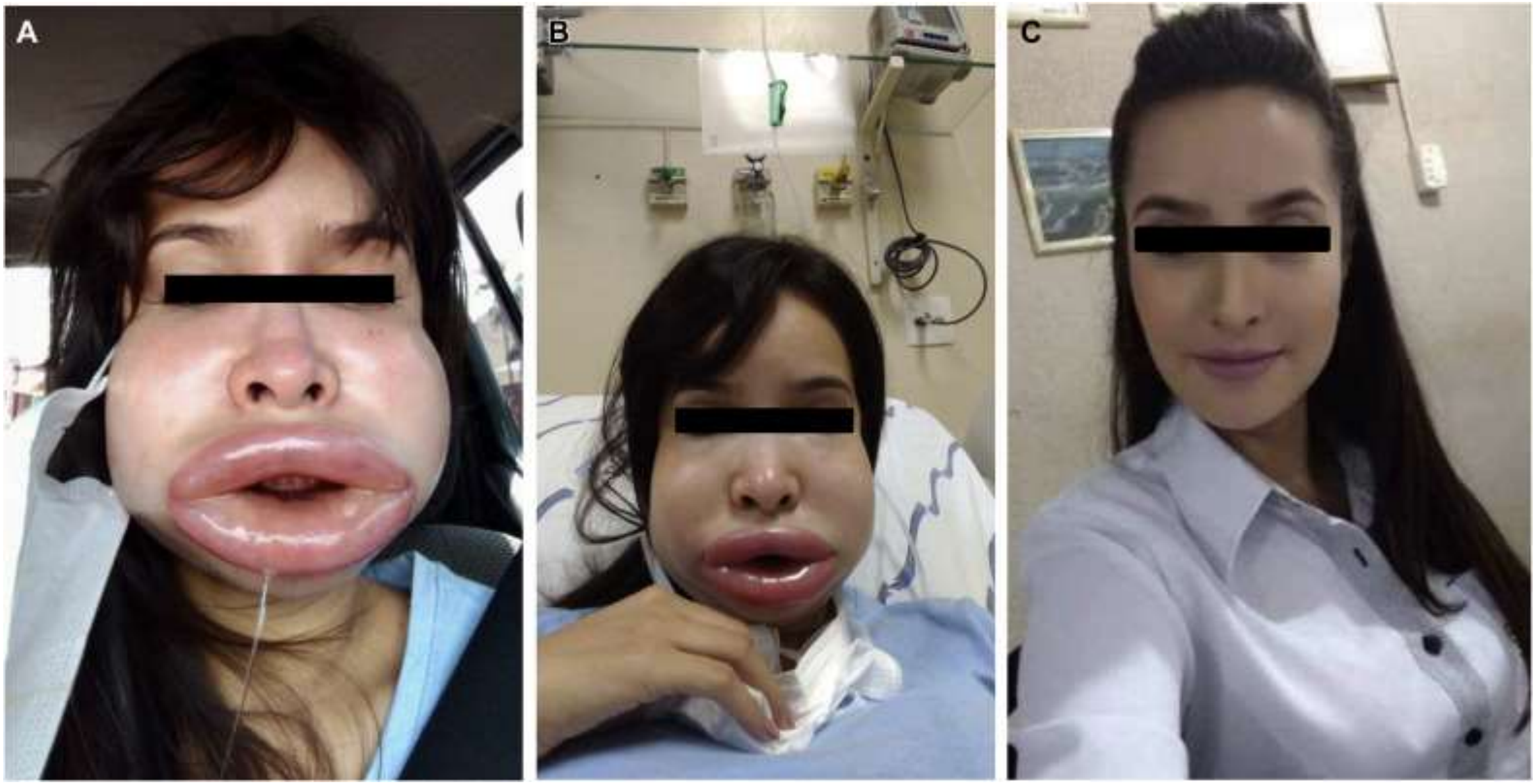
Complement deficiencies are rare (≤ 2%); they include isolated deficiencies of complement components or inhibitors and may be hereditary or acquired. Hereditary deficiencies are autosomal recessive except for deficiencies of C1 inhibitor, which is autosomal dominant, and properdin, which is X-linked.
The deficiencies result in defective opsonization, phagocytosis, and lysis of pathogens and in defective clearance of antigen-antibody complexes.

Complement Deficiencies

Disorder	Inheritance	Clinical Findings
C1	Autosomal recessive	SLE
C2	Autosomal recessive	SLE, recurrent pyogenic infections with encapsulated bacteria (especially pneumococcal) that start in early childhood, other autoimmune disorders (eg, glomerulonephritis, polymyositis, vasculitis, IgA-associated vasculitis, Hodgkin lymphoma)
C3	Autosomal recessive	Recurrent pyogenic infections with encapsulated bacteria that start at birth, glomerulonephritis, other antigen-antibody complex disorders, sepsis
C4	Autosomal recessive	SLE, other autoimmune disorders (eg, IgA nephropathy, progressive systemic sclerosis, IgA-associated vasculitis, type 1 diabetes mellitus, autoimmune hepatitis)
C5, C6, C7, C8, C9 (membrane attack complex)	Autosomal recessive	Recurrent *Neisseria meningitidis* and disseminated *N. gonorrhoeae* infections

Complement deficiencies in the MBL pathway		
MBL	Autosomal recessive	Recurrent pyogenic infections with encapsulated bacteria that start at birth; unexplained sepsis; increased severity of infection in secondary immunodeficiencies due to corticosteroid use, cystic fibrosis, or chronic lung disorders
MASP-2	Unknown	Autoimmune disorders (eg, inflammatory bowel disease, erythema multiforme), recurrent pyogenic infections with encapsulated bacteria (eg, *Streptococcus pneumoniae*)
Complement deficiencies in the alternative pathway		
Factor B	Autosomal recessive	Pyogenic infections
Factor D	Autosomal	Pyogenic infections
Properdin	X-linked	Increased risk of fulminant neisserial infection

Complement regulatory protein deficiencies		
C1 inhibitor	Autosomal dominant	Angioedema
Factor I	Autosomal codominant	Same as C3 deficiency
Factor H	Autosomal codominant	Same as C3 deficiency Hemolytic-uremic syndrome
Decay accelerating factor	Autosomal recessive	Paroxysmal nocturnal hemoglobinuria
Complement receptor (CR) deficiencies		
CR1	Acquired	Secondary finding in immune (antigen-antibody) complex–mediated disease
CR3	Autosomal recessive	Leukocyte adhesion deficiency syndrome (recurrent *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections)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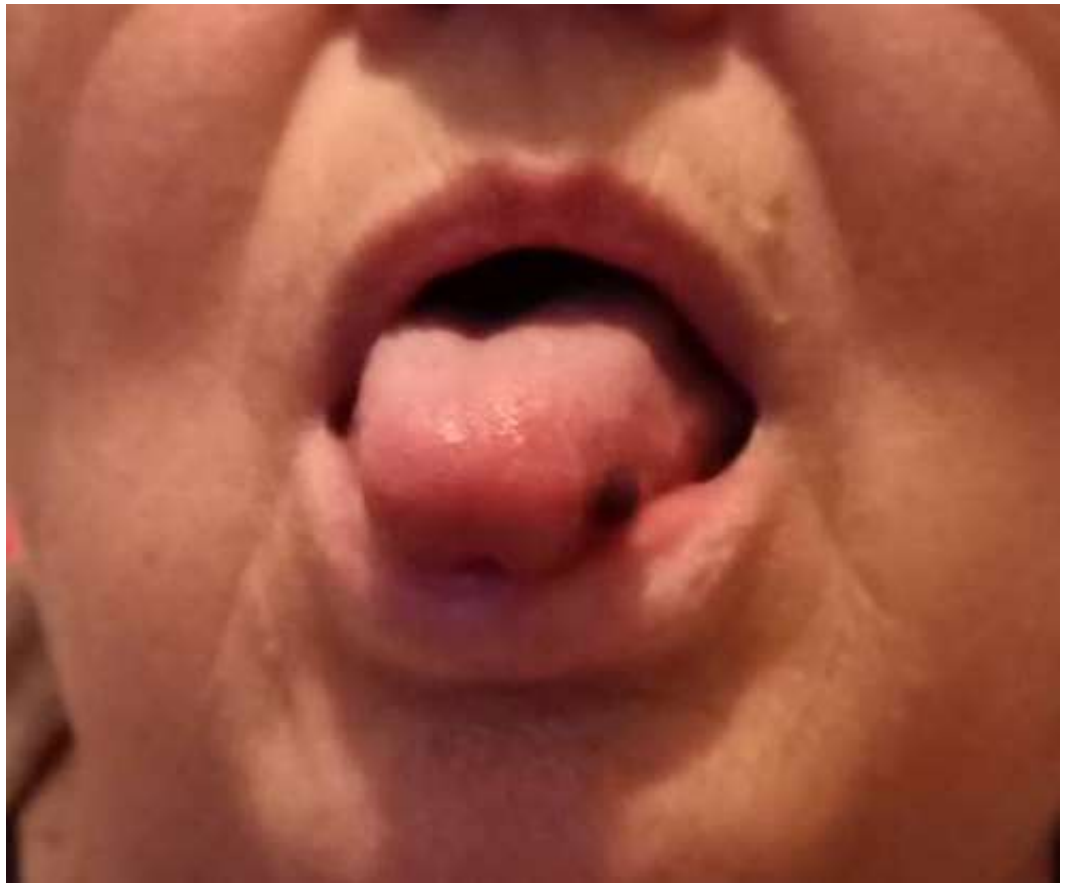

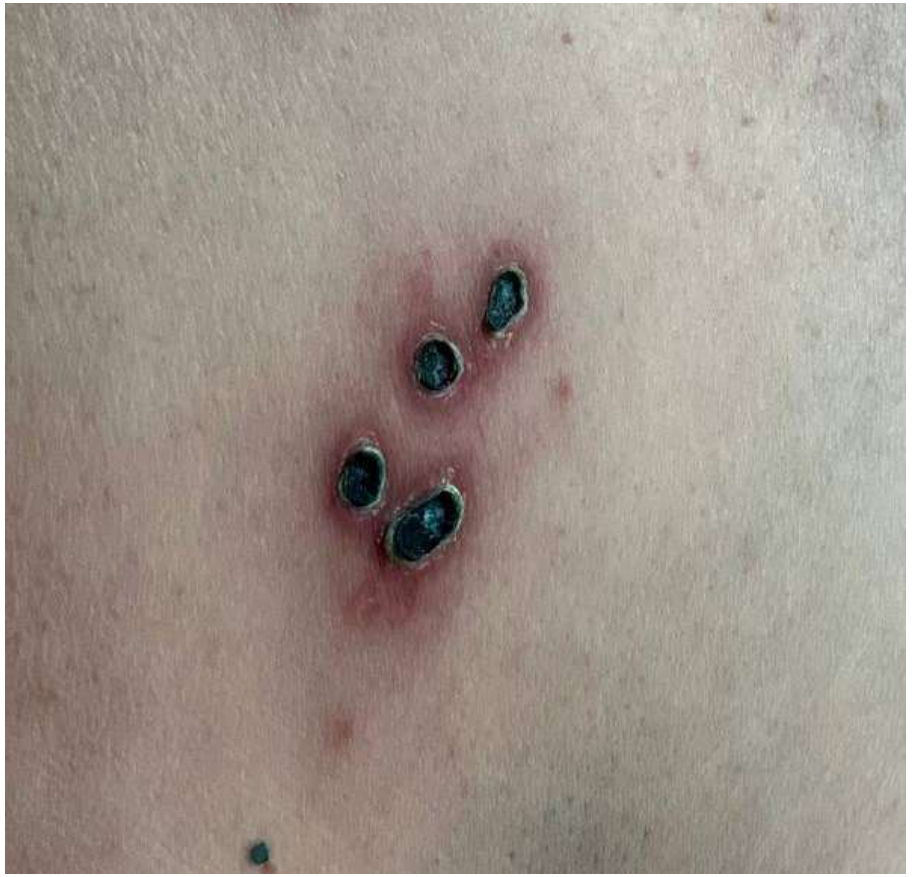

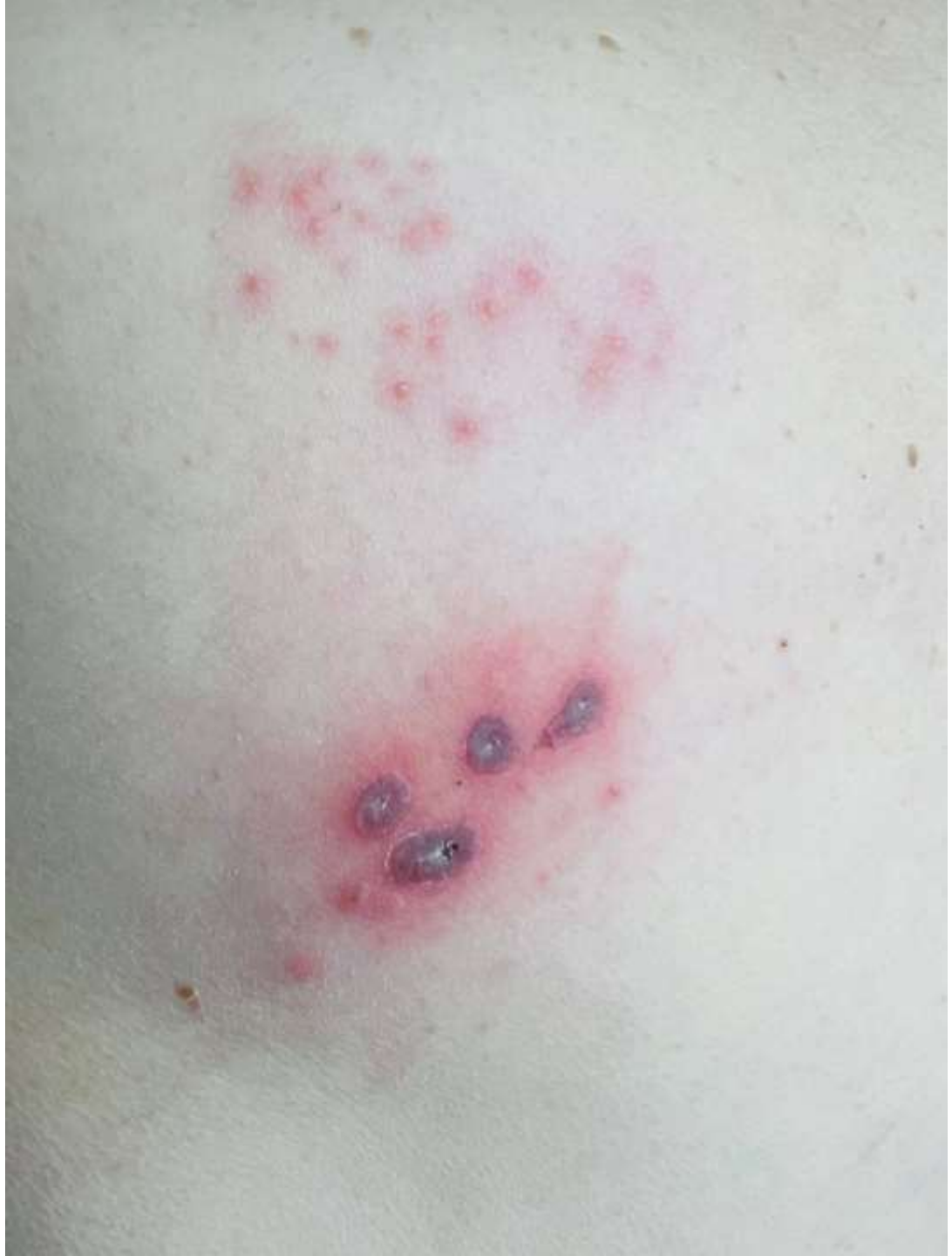

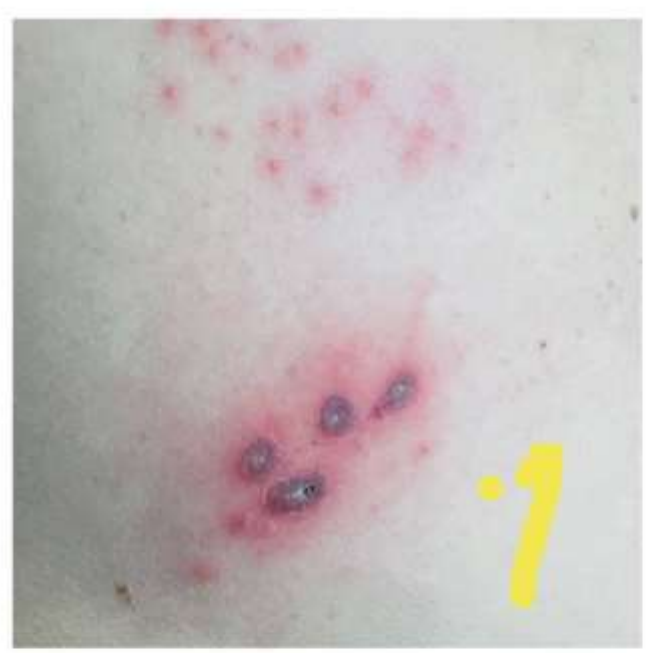
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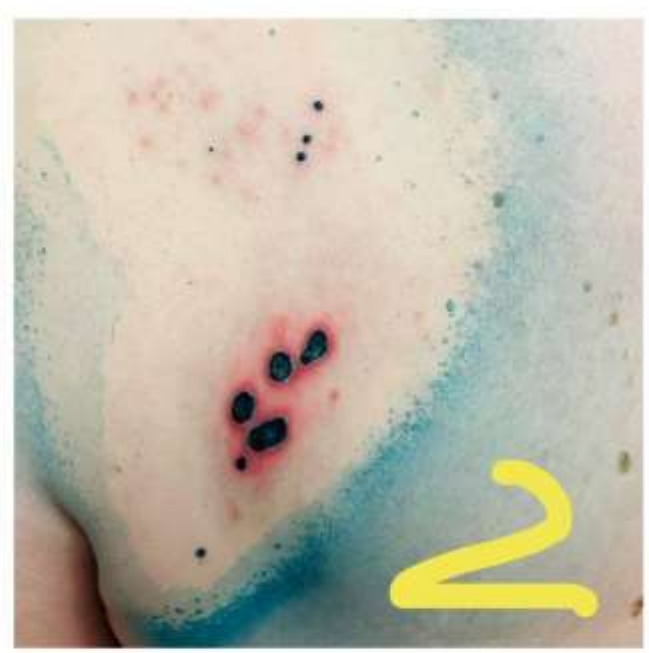
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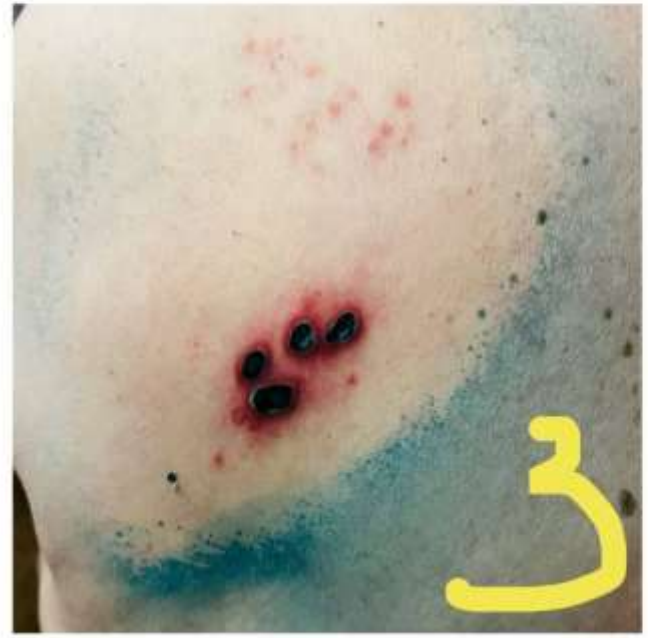
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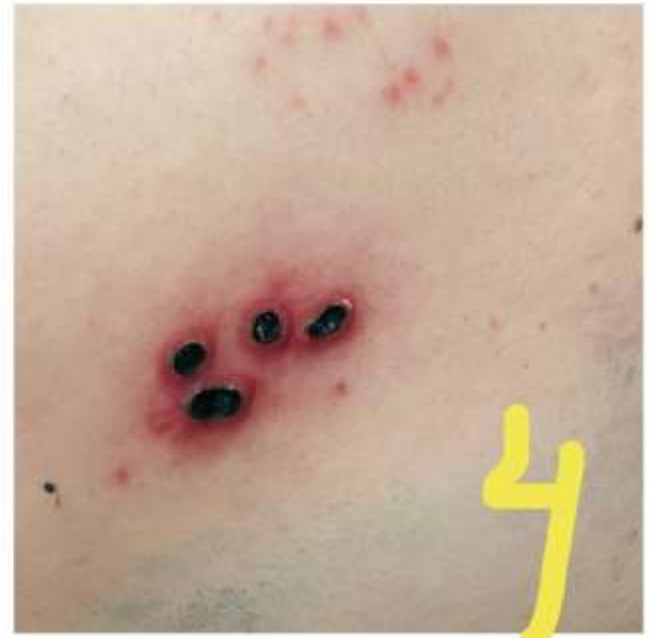
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В-клітинна ланка (В1-, В2-, В-клітини пам'яті)			
Первинна проба: венозна кров			
Лімфоцити (CD45++CD14-)	**5.28***	x10*9/л	1,0 - 2,8
Лімфоцити (CD45++CD14-) %	**65.39***	%	19 - 37
Загальні В-лімфоцити (CD45+CD19+)	**4.223***	x10*9/л	0.1 - 0.4
Загальні В-лімфоцити (CD45+CD19+) %	**79.93***	%	7 - 19
В1-клітини (аутореактивні) (CD45+CD19+CD5+)	**98.97***	%	4 - 17
В2-клітини (наївні) (CD45+CD19+CD5-CD27-)	**0.76***	%	82 - 96
В-клітини пам`яті (CD45+CD19+CD5-CD27+)	**0.27***	%	22 - 40

The most serious consequences are

- Recurrent infection, which is due to defective opsonization
- Autoimmune disorders (eg, SLE, glomerulonephritis), which is due to defective clearance of antigen-antibody complexes.

A deficiency in a complement regulatory protein causes hereditary angioedema.

Complement deficiencies can affect the classical and/or alternate pathways of the complement system. The alternate pathway shares C3 and C5 through C9 with the classical pathway but has additional components: factor D, factor B, properdin (P), and regulatory factors H and I.

X-linked Agammaglobulinemia (Bruton Disease)

X-linked agammaglobulinemia is characterized by low levels or absence of immunoglobulins and absence of B cells, leading to recurrent infections with encapsulated bacteria.

X-linked agammaglobulinemia is a primary immunodeficiency disorder that involves humoral immunity deficiencies. It results from mutations in a gene on the X chromosome that encodes Bruton tyrosine kinase (BTK). BTK is essential for B-cell development and maturation; without it, maturation stops before the B-cell stage, resulting in no mature B cells and hence no antibodies.

As a result, male infants have very small tonsils and do not develop lymph nodes; they have recurrent pyogenic lung, sinus, and skin infections with encapsulated bacteria (eg, Streptococcus pneumoniae, Haemophilus influenzae). Patients are also susceptible to persistent central nervous system (CNS) infections resulting from live-attenuated oral polio vaccine and from echoviruses and coxsackieviruses; these infections can also manifest as progressive dermatomyositis with or without encephalitis. Risk of infectious arthritis, bronchiectasis, and certain cancers is also increased.

With early diagnosis and appropriate treatment, prognosis is good unless viral infections of the central nervous system develop.

Diagnosis

Low immunoglobulin levels and absent B cells
Genetic testing

Diagnosis of X-linked agammaglobulinemia is by detecting low (at least 2 standard deviations below the mean) levels of immunoglobulins (IgG, IgA, IgM) and absent B cells (< 1% of all lymphocytes are CD19+ cells, detected by flow cytometry). Transient neutropenia may also be present.

Genetic testing can be used to confirm a diagnosis but is not required. It is usually recommended for 1st-degree relatives. If the mutation has been identified in family members, mutational analysis of chorionic villus, amniocentesis, or percutaneous umbilical cord blood samples can provide prenatal diagnosis.

Treatment

Immune globulin replacement therapy

Treatment of X-linked agammaglobulinemia is immune globulin replacement therapy.

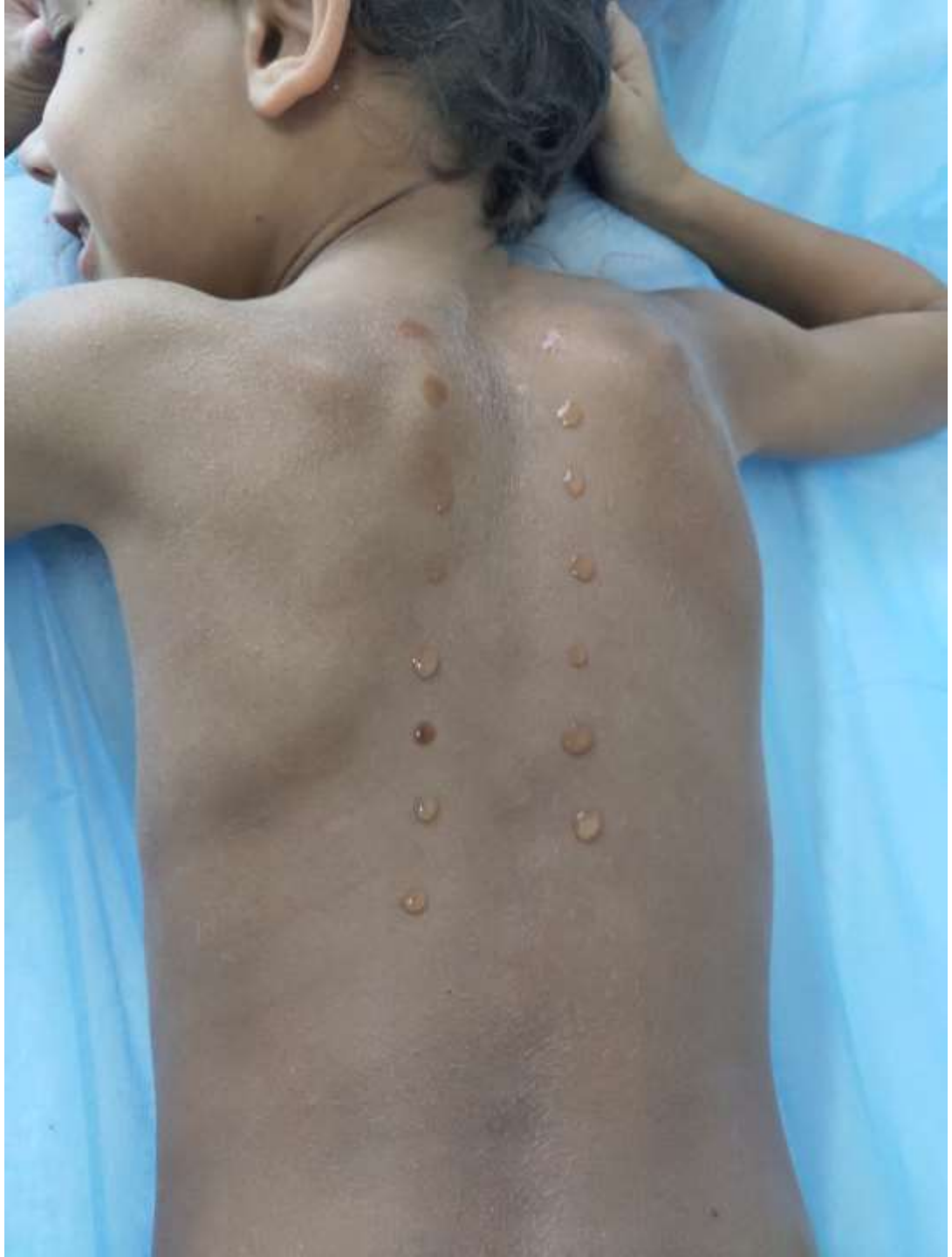
Prompt use of adequate antibiotics for each infection is crucial; bronchiectasis may require frequent rotation of antibiotics.

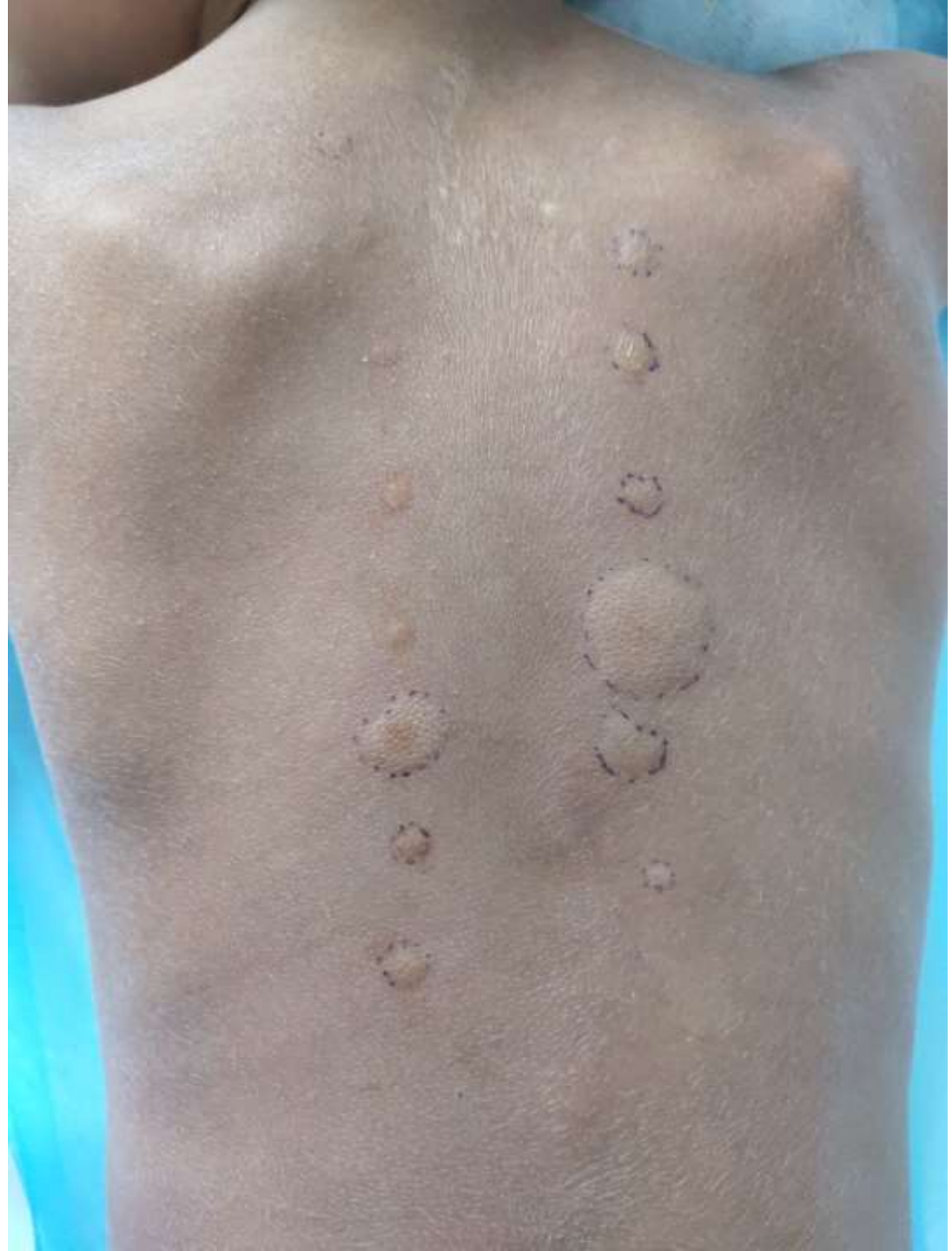
Live-virus vaccines are **contraindicated**

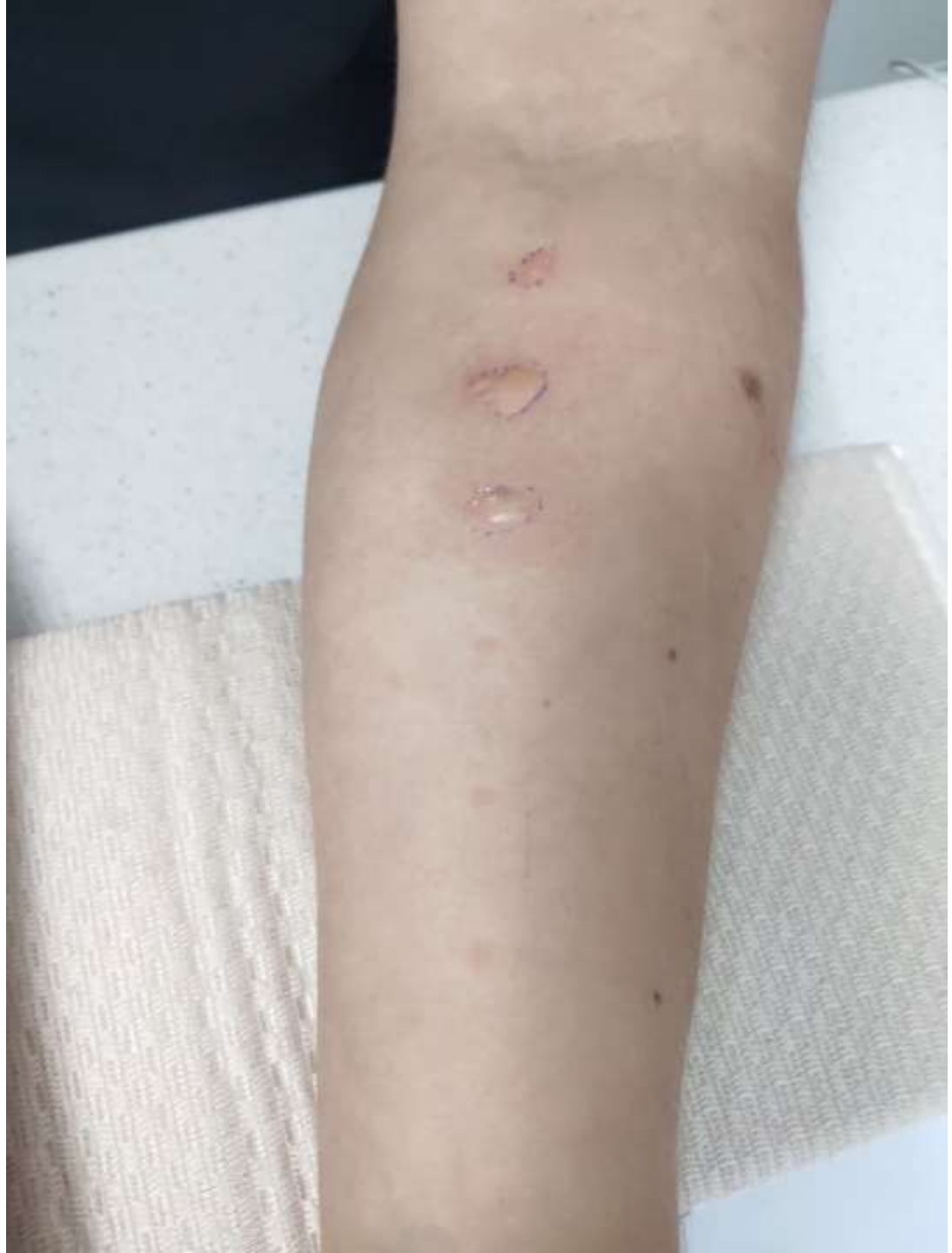
Key Points

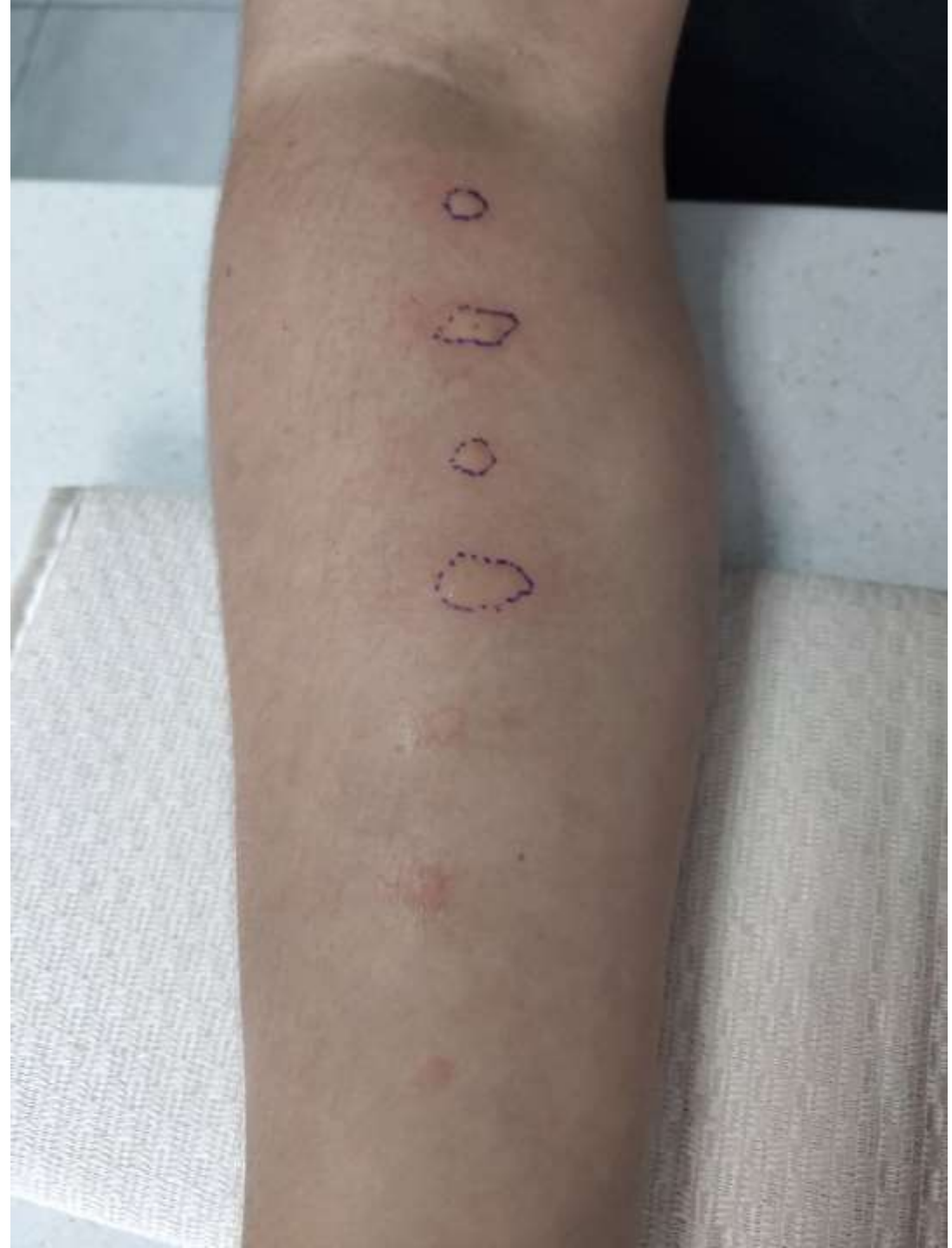
- Consider a primary immunodeficiency if infections are unusually frequent or severe, particularly if they occur in family members, or if patients have thrush, oral ulcers, periodontitis, or certain skin lesions.
- Do a complete physical examination, including the skin, all mucous membranes, lymph nodes, spleen, and rectum.
- Begin testing with CBC (with manual differential), quantitative Ig levels, antibody titers, and skin testing for delayed hypersensitivity.
- Select additional tests based on what type of immune defect is suspected (humoral, cellular, phagocytic cell, or complement).
- Test the fetus (eg, using fetal blood, chorionic villus sampling, or cultured amniotic cells) if family members are known to have an immunodeficiency disorder.
- Teach patients how to avoid infections, **give indicated vaccines,** and prescribe prophylactic antibiotics for patients with certain disorders.
- Consider immune globulin replacement for antibody deficiencies and hematopoietic stem cell transplantation for severe immunodeficiencies, particularly T-cell immunodeficiencies.

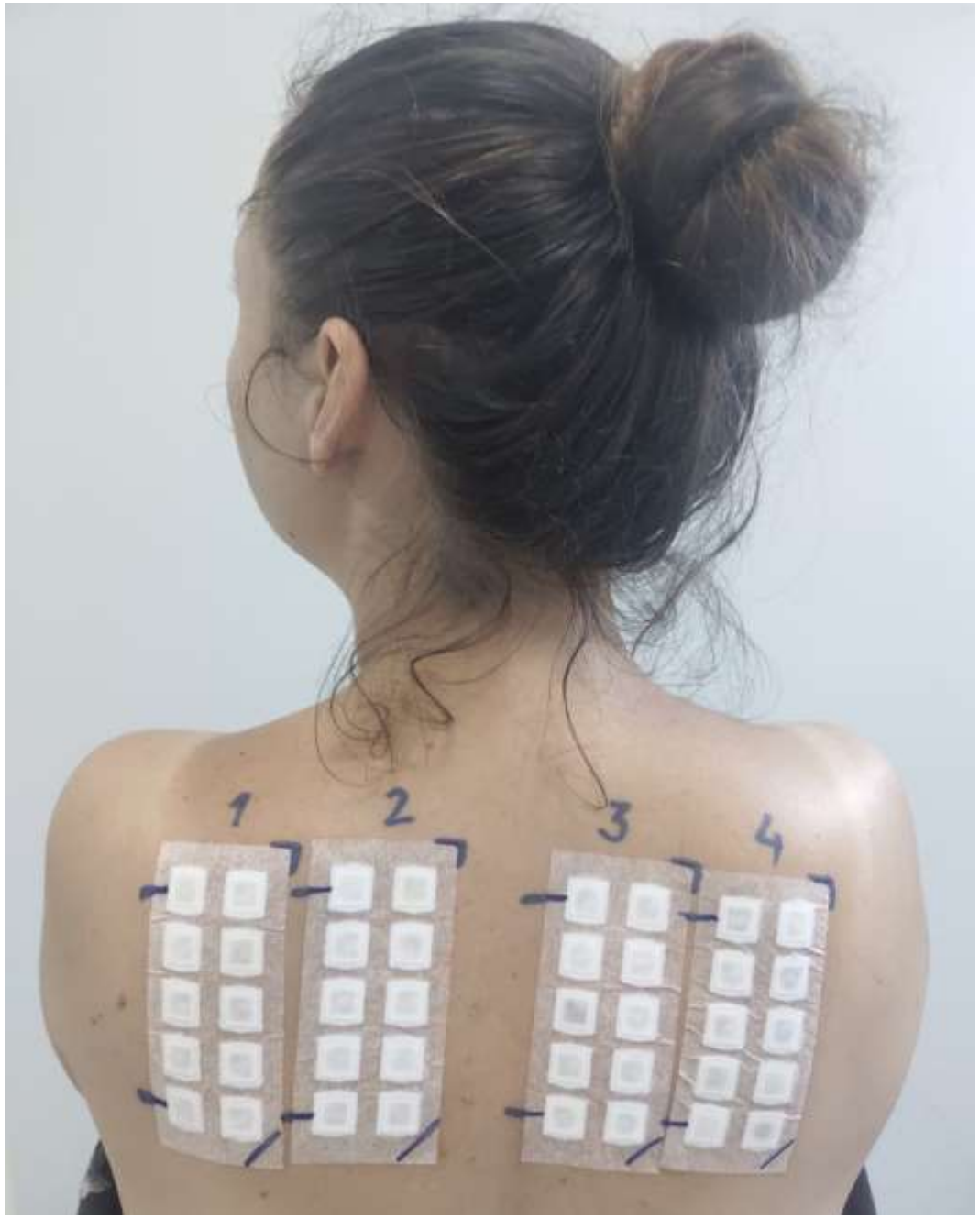
SKIN-PRICK TESTING



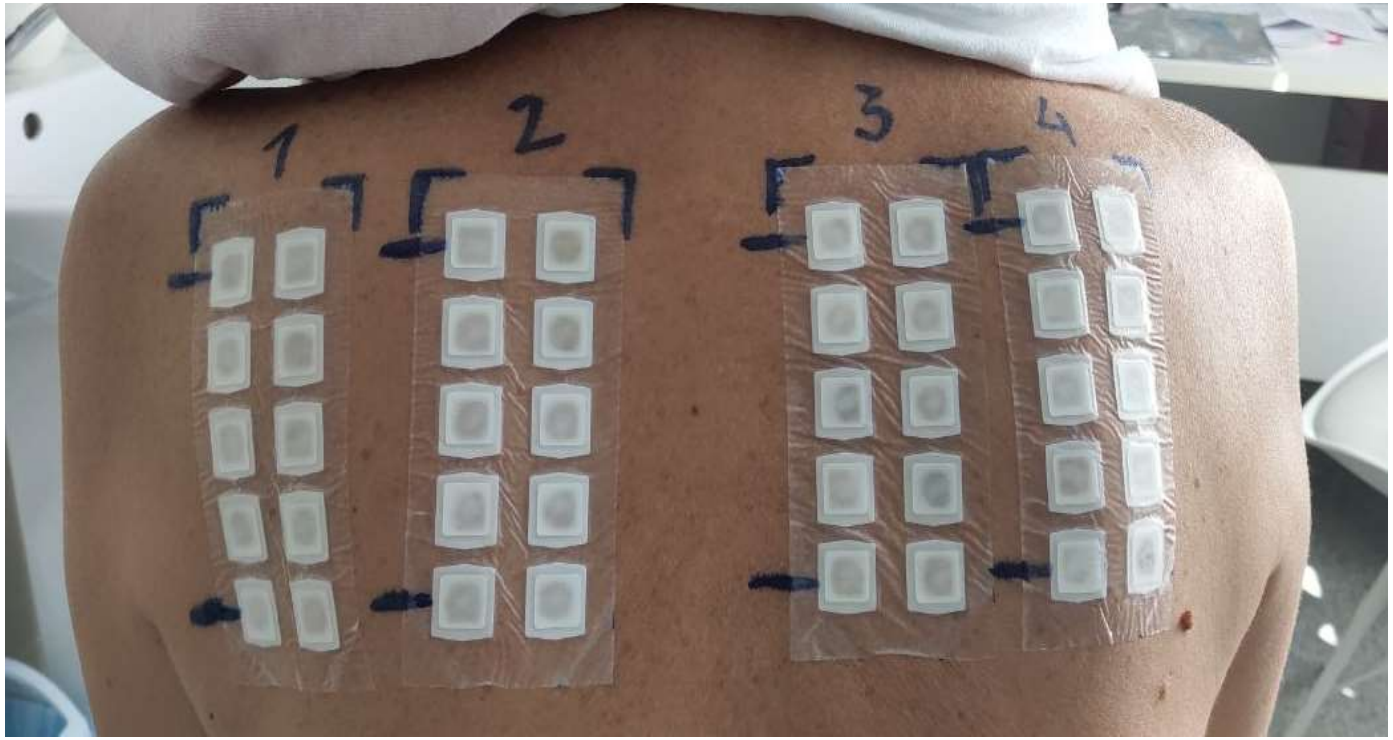








PATCH TESTING
for Delayed type
of hypersensitivity



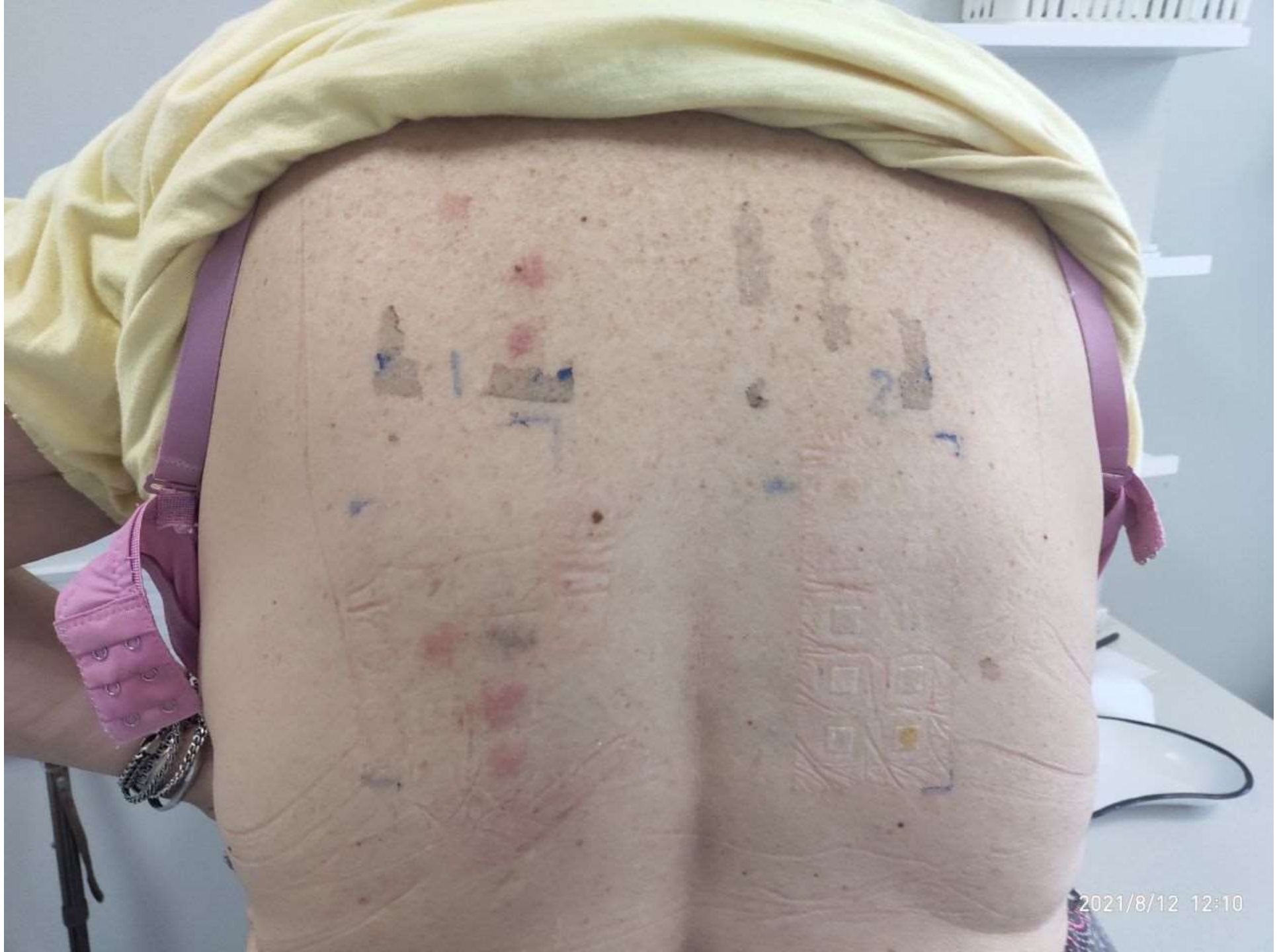

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Figure 1 Tuberculin syringe with 25G needle and flat end plunger drawn up with 0.02 ml solution

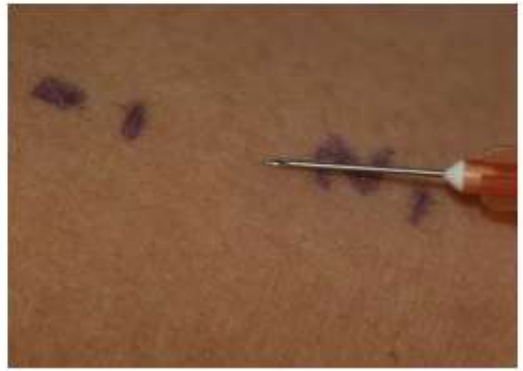

Figure 2 Inject with the bevel of the needle facing upwards

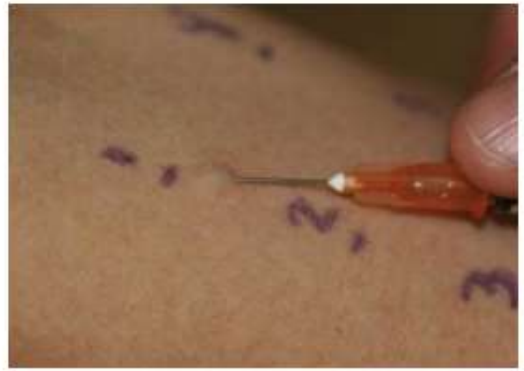

Figure 3 Pierce skin tangentially in the upper dermis (at about 10° angle to the skin surface) and inject the whole volume (0.02 ml)

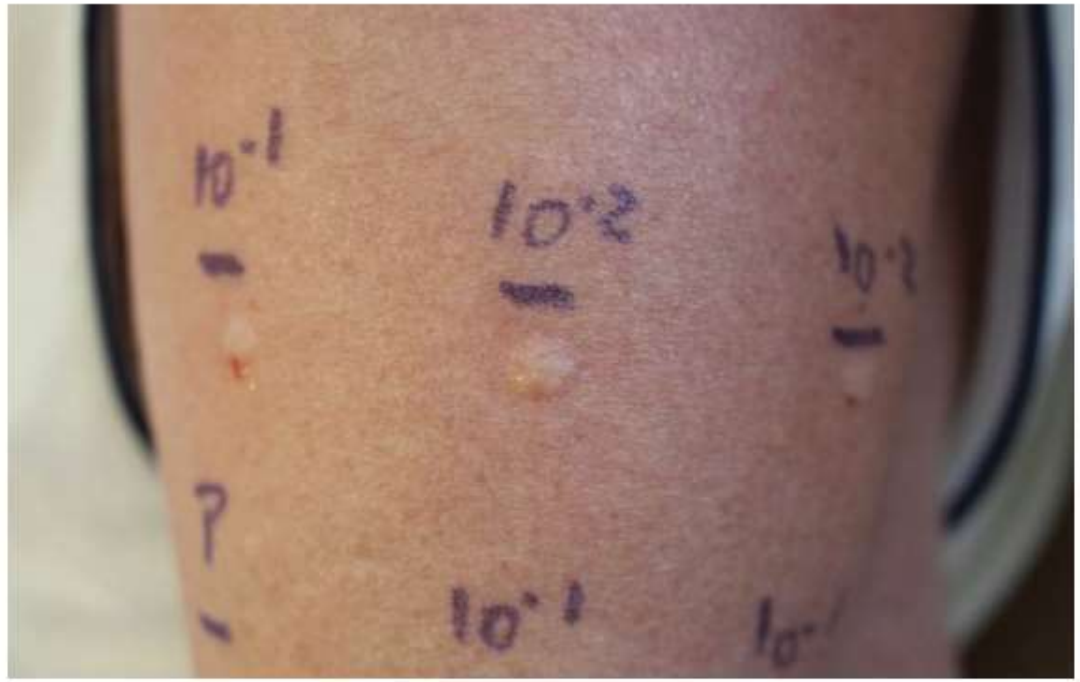

Figure 4 The injection wheal has a specific feature in "peau d'orange"