REVIEW ARTICLE

CONTENTS

Infectious exanthemas in clinical practice

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ABSTRACT

Aim: Analyze the causes and mechanisms of development of exanthems, provide a classification of the morphological elements and characterize clinical manifestations of rash in patients with infectious diseases based on a review of available literature data.

Materials and Methods: The authors analyzed the current literature sources, including a description of exanthema syndrome and a discussion of the features of rashes in various infectious diseases.

Conclusions: As a result of the analysis of existing literature data, it was established that exanthema syndrome is associated with various diseases, disorders and pathological conditions, characterized by a variety of clinical manifestations, which requires clinical differential diagnosis and subsequent laboratory confirmation. Comprehensive knowledge of the causes, mechanisms of development, as well as the clinical manifestations of skin rash will contribute to the development of an improved algorithm for diagnosis and treatment of the diseases accompanied by exanthema syndrome, as well as optimization of therapeutic tactics.

KEY WORDS: exanthema syndrome, classification, infectious diseases, diagnostic algorithm

Wiad Lek. 2025;78(1):168-176. doi: 10.36740/WLek/197135 DOI

INTRODUCTION

Exanthema syndrome includes the presence of rashes on the surface and/or in deeper layers of the skin, is very common in the practice of physicians of many specialties and is of key importance in clinical diagnosis, including differential diagnosis, in the context of various diseases and pathologic conditions [1-3]. The war in Ukraine started by russia is an unprecedented stressor that leads to an increased incidence of many diseases that can be accompanied by exanthema syndrome [4, 5].

The relevance of exanthema syndrome also lies in the fact that very often the rash has polymorphic manifestations, and sometimes even atypical signs. This complicates the timely correct diagnosis, since at the prehospital stage the diagnosis is made mainly on the basis of the clinical picture, without available laboratory confirmation [2, 6, 7].

Therefore, systematization and analysis of existing literature data is appropriate for further development of an improved algorithm for diagnosis and treatment of diseases accompanied by exanthema syndrome.

AIM

Analyze the causes and mechanisms of development of exanthems, provide a classification of morphological elements and characterize the clinical manifestations of rash in infectious diseases based on available literature data.

MATERIALS AND METHODS

The authors analyzed the current literature sources, including a description of exentematous syndrome and a discussion of the features of rashes in various infectious diseases.

REVIEW AND DISCUSSION

Usually, exanthema of infectious nature occurs due to growth of the infectious agent in the skin, its transfer by plasma or infected cells (leukocytes, lymphocytes) into the skin vessels, as well as hypersensitivity reactions. In most infectious exanthems, the appearance of the rash indicates the development of immunologic reactions (antigen-antibody interaction). As a consequence, the following processes occur: swelling of collagen fibers, vascular dilation, cellular infiltration and the appearance of various morphological elements of rashes [1, 6, 8]. Depending on the cause of occurrence, exanthemas of an infectious nature are classified as follows [2, 3, 9]:

- viral (measles, rubella, scarlet fever, chicken pox, COVID-19, hemorrhagic fevers, herpes infections

(including infectious mononucleosis), HIV infection, hepatitis B, enteroviral, parvoviral diseases, etc.);
- bacterial (meningococcal infection, typhoid-paratyphoid diseases, rickettsiosis, leptospirosis, ersiniosis, erysipelas, Lyme disease, syphilis, felinosis, staphylococcal infection, molluscum contagiosum, etc.);
- fungal (histoplasmosis, coccidiomycosis, actinomycosis, etc.);
- parasitic (leishmaniasis, ascariasis, enterobiasis, echinococcosis, opisthorchiasis, trichinosis, toxocariasis, scabies, etc.).

In addition, in the context of differential diagnosis, the clinician should remember the following types of exanthems:
- exanthemas in systemic connective tissue diseases (rheumatic fever, systemic lupus erythematosus, systemic scleroderma, dermatomyositis, systemic vasculitis, juvenile rheumatoid arthritis, etc.);
- exanthema in malignant diseases (including during radiation or chemotherapy);
- exanthems associated with insect bites;
- exanthemas of an allergic nature (associated with taking medications, foods, etc.): urticaria, allergic dermatitis, DRESS syndrome, Lyell's syndrome, Steven-Johnson syndrome, etc.;
- exanthemas caused by the administration of vaccines and serums.

There are *primary morphological elements* that arise on intact skin and are classified as non-hollow and hollow. Primary non-hollow elements include include spots, papules, blisters, tubercles, and nodules, and primary hollow elements include vesicles, pustules, and bullae. *Secondary morphological elements* are formed as a result of the evolution of primary elements, their damage or infection. Secondary elements include scales, crusts, scars, erosions, ulcers, abrasions, cracks, vegetations and striae [2, 3].

EXANTHEMA IN INFECTIOUS DISEASES

MEASLES

The main cutaneous syndrome of measles is a maculopapularexanthema with uneven festoon-like edges. This exanthema is prone to fusion, abundant, bright, sometimes has a hemorrhagic component. The rash appears on the unchanged skin on the fourth or fifth day from the onset of the disease against the background of the second wave of fever, increased intoxication and respiratory and catarrhal syndrome. A pathognomonic sign of a rash in measles is staging: on the first day, the rash appears behind the ears, on the nose; then the rash thickly covers the face, neck, upper chest and shoulders; on the second day, the rash spreads to the trunk and proximal areas of the upper extremities; on the third day, the distal areas of the upper and lower extremities are affected by the rash. The peculiar evolution of the elements of the rash is typical: initially, small papules and spots appear (diameter 3-5 mm), which increase very quickly in size up to 10-15 mm; some spots (especially on the face and upper trunk) merge into a continuous erythematous surface. The exanthema begins to regress from the third day in the order of its appearance on the skin with the formation of secondary elements: pigmentation and bran-like peeling. For the clinical diagnosis of measles, the following symptoms should also be taken into account: acute onset with high body temperature; conjunctivitis, scleritis, blepharitis, lacrimation (worldview, up to blepharospasm); cough, runny nose; on the second day of the disease, Koplik's spots occur on the mucous membrane of the cheeks opposite the small molar teeth (white formations with a diameter of 1 mm, surrounded by a zone of hyperemia); enanthema in the form of pink spots on the mucosa of the hard and soft palate may also develop. Spotted exanthema may appear as a variant of the normal post-vaccination period in children vaccinated with live measles vaccine. On days 6-10 after vaccination, in combination with non-confluent exanthema, the following symptoms sometimes occur: low-grade fever, runny nose, cough, conjunctivitis (within 2-3 days). The staging of rashes, like the Koplik's spots, is not typical for post-vaccination exanthema. For specific diagnostics: cytologic examination (cytoscopy) of swabs from oropharynx (detection of multinucleated giant cells typical for measles); serologic methods (increase in the titer of specific IgG antibodies in dynamics by 4 or more times, detection of specific IgM antibodies to measles virus) [7, 9-11].

RUBELLA

The leading skin syndrome of acquired rubella is an exanthema that appears on the first or second day from the onset of the disease, simultaneously on different parts of the body with predominant localization on the face, extensor surfaces of the extremities and buttocks. The rash in rubella is small-spotted, pale pink, abundant, not prone to coalescence, located on a normal skin background. The rash persists for 2-4 days, occasionally for 5-7 days and disappears without trace. For the differential diagnosis of rubella, the following facts should also be taken into account: enlargement of the occipital and posterior cervical lymph nodes (soft, somewhat painful on palpation, size 1-2 cm); no changes in the mucous membranes of the oral cavity and oropharynx. In 20-30% of cases, rubella can develop without a rash. Such forms are not clinically recognized,

but the possibility of such a course should be remembered when monitoring a pregnant woman in a rubella outbreak. The diagnosis of rubella is confirmed using serological methods (an increase in the titer of specific IgG antibodies over time by four or more times, the detection of specific IgM to the rubella virus); molecular methods (detection of rubella virus RNA in biological materials (blood, urine, saliva, cerebrospinal fluid) by PCR [2, 7, 12].

SCARLET FEVER

The leading skin syndrome of scarlet fever is a small-point rash accompanied by some features: detection of rashes on the background of hyperemic skin; mainly on the bending surfaces of the extremities, lateral parts of the chest, abdomen, internal and posterior surfaces of the thighs and in places of natural folds of the skin (axillary, axillary, elbow, knee); pale nasolabial triangle; dryness and roughness of the skin during the rash; persistent white dermographism due to damage to the autonomic nervous system; acute tonsillitis syndrome (catarrhal, follicular, lacunar) in the first hours of the disease; regional lymphadenitis with damage to the anterior cervical lymph nodes; in severe course of the disease - Pastia's symptom (hemorrhagic strips in the natural folds of the skin – an additional symptom for the diagnosis of the scarlet after the disappearance of the small-point rash; after regression of exanthema - fine bran-like peeling of the skin on the trunk and earlobes, as well as leaf-like lamellar peeling on the fingers and toes, palms and soles are observed; ; changes in the tongue (on the first day of illness, the tongue is covered with a thick white coating; starting from the second day, the tongue begins to clear of plaque and becomes scarlet with enlarged papillae, the so-called "raspberry" or "strawberry" tongue). The reduction in the main clinical symptoms of scarlet fever usually occurs in the following sequence: fever and symptoms of intoxication (on day 2-3), lymphadenitis (on day 3-4), rash (on day 1-5), tonsillitis (on day 6-7), changes in the tongue (from day 10). The degree of intoxication syndrome with scarlet fever may vary, but usually the modern course of scarlet fever is not accompanied by intoxication and a significant increase in body temperature. The diagnosis of scarlet fever is confirmed by bacteriological examination of mucus from the oropharynx (isolation of group A β-hemolytic streptococcus), as well as by serological methods [2, 7, 9, 13, 14].

CHICKENPOX

The leading skin syndrome of chickenpox is vesicular exanthema. Vesicles are single-chambered, round or oval, 0.2-0.5 cm in diameter, surrounded by a rim of hyperemia, located superficially on a non-infiltrated base with transparent contents (on the face, hairy part of the head, trunk and limbs), appear on the first or second day of the disease. On the skin, elements of rashes at different stages of development can be observed: macules, papules, vesicles, crusts. For differential diagnosis, the following facts are important: absence of rashes on the palms and soles, localization of vesicles on the hairy part of the head, undulating fever (the appearance of new rashes is accompanied by an increase in body temperature), moderate symptoms of intoxication. The diagnosis is confirmed by detection of the virus antigen in smear from the contents of vesicles); ELISA (detection of specific IgM in blood); PCR method (detection of varicella virus RNA in biological materials: blood, cerebrospinal fluid, vesicle contents) [2, 7, 11, 15, 16].

HSV ½ INFECTION

Herpetic skin lesions are the most common form of the disease caused by the herpes simplex virus ½ types. The rash appears in the form of grouped, small (up to 0.1 cm in diameter), tense vesicles on an edematous, hyperemic base; The rashes are localized mainly on the skin around the mouth, wings of the nose, ears, and red border of the lips. In some cases, rashes may appear on the mucous membrane of the oral cavity, larynx, tonsils, conjunctiva, sometimes in the form of herpetic stomatitis or gingivostomatitis. Skin lesions may be localized or widespread with recurrent rashes. Hyperesthesia, itching, burning and other subjective sensations precede the appearance of rashes. After the vesicles have ruptured or dried, secondary elements in the form of crusts are formed. The foci disappear on days 7-9.

The generalized form of herpes, herpetic eczema, occurs mainly in individuals with atopic dermatitis, dermatoses, and also with HIV infection. Abundant vesicular eruptions appear in areas of eczematous skin and quickly spread to unaffected skin. Often the elements of the rash merge and burst to form a solid crust. Secondary elements of the exanthema after rejection of the crust look like pink spots or scars. High fever with severe general intoxication syndrome is typical for this disease. The diagnosis is confirmed by the isolation of HSV ½ in cell culture (virological method; material - vesicle fluid, cervical smear, vaginal discharge), detection of HSV½ DNA (PCR method; material - vesicle fluid, cervical smear, vaginal discharge, cerebrospinal fluid); serological tests (specific antibodies against HSV½ appear in the blood within a few weeks after infection) [1, 2, 7].

COVID-19

COVID-19 infection primarily causes interstitial pneumonia and respiratory failure [17], but it is often associated with skin manifestations as well. Lesions of the mucous membranes and skin in COVID-19 can occur at the onset of the disease or during its progression. The pathogenesis of skin rashes may include vasculitic and inflammatory skin rashes. They can be associated with both strong immune response and directly high SARS-CoV2 viral load. These skin manifestations can be divided into several groups: skin rashes similar to frostbite (e.g., toes in COVID); skin rashes similar to urticaria; maculopapular lesions; vesicular rashes; purpura, reticular livedo, and necrotic lesions; urticarial vasculitis, and others such as alopecia and herpes zoster. Detection of SARS-CoV-2 RNA by PCR is of leading importance for confirming the diagnosis of COVID-19 [18].

INFECTIOUS MONONUCLEOSIS

Exanthema in EBV-infectious mononucleosis occurs in 16-25% of patients. The rash appears on the 3rd-14th day of the disease and can be polymorphic: spotty, spotty-papular, roseollous. The rash persists on the skin for 4-10 days, with the possible appearance of secondary elements of the rash in the form of pigmentation. For diagnosis, other clinical signs of infectious mononucleosis are also important: prolonged fever and other symptoms of intoxication; puffiness of the face with difficulty breathing through the nose without severe catarrhal phenomena; generalized lymphadenopathy with predominant enlargement of the posterior cervical lymph nodes, which can reach 10-15 mm in diameter and cause neck deformation; hepatosplenomegaly; tonsillitis syndrome; jaundice, pain in the abdominal area along the mesentery can occur with severe and atypical course of the disease; leukocytosis or normocytosis with lymphomonocytosis and atypical mononuclear cells, relative and absolute neutropenia, moderately increased ESR. The diagnosis is confirmed by the detection of specific antibodies to Epstein-Barr virus antigens in the blood by ELISA and EBV DNA in PCR [11, 12, 20].

ENTEROVIRUS EXANTHEMA (HAND, FOOT, AND MOUTH DISEASE)

One of the leading syndromes of these diseases is polymorphic rash (spotty or spotty-papular, pink, may be fine-pointed), which appears simultaneously on an unchanged skin background on the 1-2 day, together with fever or after its reduction (on the 3-5 day). The predominant localization of rashes – the skin of the face and trunk, less often – the extremities. The exanthema persists for 1-2 days, disappears without a trace. This disease is also characterized by high fever, which can be two-wave, and moderate symptoms of intoxication. Specific diagnostics is based on serological (an increase in the titer of specific IgG antibodies over time by four or more times) and molecular methods (detection of enterovirus RNA in blood, urine, feces, cerebrospinal fluid by PCR) [9, 21, 22].

EXANTHEMA SUBITUM («PSEUDO-RUBELLA», SIXTH DISEASE) CAUSED BY HHV6

The rash in this pathological condition is characterized by the appearance of spotty, pale pink elements with a diameter of 2-5 mm, which do not merge with each other and are located on an unchanged skin background, on days 3-5 of the disease against the background of a critical decrease in body temperature. Exanthema occurs simultaneously, mainly on the torso, neck, to a lesser extent on the face and limbs, persists for 2-3 days and disappears without a trace. To diagnose Exanthema subitum, it is necessary to take into account other characteristic signs of infection caused by HHV_6: acute onset, rapid increase in body temperature to 38-40 °C, moderate symptoms of general intoxication, mild respiratory catarrhal syndrome, possible generalized lymphadenopathy (mainly of the cervical, axillary and axillary groups of lymph nodes). ELISA (determination of specific IgM titer for diagnosis of acute or reactivation of chronic infection) and PCR (detection of DNA in peripheral blood lymphocytes or other tissues) are most often used to confirm the diagnosis. [11, 23].

PARVOVIRAL B19 INFECTION (INFECTIOUS ERYTHEMA)

Infectious erythema (fifth disease) is characterized by the appearance of spotty or spotty-papular bright red rashes on the face, which merge on the cheeks, forming a bright erythema, similar to traces of slaps (on the nose in the form of a butterfly). Exanthema appears on the 2-5th day of the disease. After 1-4 days, a secondary erythematous maculopapular rash on the trunk and extremities, including the palms and soles, with itching begins to appear. The exanthema is mainly localized on the extensor (dorsal) surfaces of the limbs, and the red color of the rash quickly turns bluish-red. With the reverse development of secondary erythema, a mesh "lace" pattern appears. Secondary rash elements disappear gradually with possible recurrence of rash elements due to a number of factors: insolation, hypothermia, bathing, etc. For the diagnosis of parvovirus

infection, it is necessary to take into account other clinical signs that appear before the onset of rashes: fever, respiratory catarrhal syndrome, nausea, diarrhea, arthralgia and arthritis. Parvovirus infection is usually confirmed by the determination of titers of specific IgM and IgG using ready-made ELISA kits. Sometimes a virus is isolated from serum or tissues, as well as viral antigens and DNA are detected by PCR [12, 24, 25].

HEMORRHAGIC FEVER WITH RENAL SYNDROME (HFRS)

HFRS is characterized by non-extensive, petechial exanthema, which may appear as streaks, reminiscent of whip marks. The rash is localized in the area of the clavicles, axillary folds, sometimes on the neck and face, appears from the 4th day of diseases and disappears without a trace. At the same time, a hemorrhagic enanthema occurs on the mucous membrane of the soft palate. HFRS is accompanied by hyperemia of the face and neck, increased blood flow to the vessels of the sclera and conjunctiva. For clinical diagnosis, the combination of hemorrhagic rash with other clinical symptoms of HFRS is important: sudden rapid onset of the disease, high fever with chills for 5-6 days, severe symptoms of intoxication (headache, pain in the eyeballs, myalgia, arthralgia), visual disturbances, pain in the abdomen and lower back, other signs of hemorrhagic syndrome (nosebleeds, hemorrhages in the sclera, hemorrhages in injection sites, hematuria), decreased diuresis from 4- 5 days, progression of acute renal failure. The absence of respiratory-catarrhal syndrome is typical for HFRS. For the purpose of specific diagnosis, ELISA (detection of specific IgM antibodies already in the early stages of the disease), immunohistochemical testing and PCR are used (detection of the virus or its particles) and, in some cases, virological testing [26, 27].

HEPATITIS B

The most common skin manifestations in hepatitis B include urticaria and Gianotti-Crosti syndrome (papular acrodermatitis, usually in childhood). Urticaria can be the main characteristic feature of the prodromal period of hepatitis B. Rashes (macular-papular or petechial) usually last for several days and precede the development of arthralgia and jaundice. Gianotti-Crosti syndrome is characterized by: erythematous-papular rash; absence of itching; symmetrical location of exanthema elements on the skin of the face, buttocks and extremities. Fresh elements continue to appear for several days and never merge. The exanthema is maintained for about 3 weeks. Within a few months, signs of lymphadenopathymay be observed. Often, the appearance of rashes is associated with a non-jaundice form of hepatitis, and the symptoms of hepatitis may occur simultaneously with the appearance of the rash or several weeks later. This variant is typical for European countries, where the Adw serotype of the hepatitis B virus is common. The specific diagnosis of hepatitis B is based on the detection of HBV DNA in serum (PCR), the determination of the HBs antigen and the spectrum of antibodies to HBV antigens [28, 29].

CONTAGIOUS MOLLUSCUM

Contagious molluscum is a viral disease characterized by the appearance of nodules ranging in size from hairpin to pea, hemispherical, having skin color or slightly pink, translucent, relatively dense. Nodules are located more often on the skin of the face, neck, as well as the trunk and extremities separately; when pressing on them a grayish-white mushy mass is secreted. In doubtful cases, the diagnosis is confirmed by microscopic examination of secretion from an element of the rash or a skin biopsy stained by the Wright or Giemsa method - the presence of inclusions (mollusc bodies) in the cytoplasm [30].

MENINGOCOCCAL INFECTION (MENINGOCOCCEMIA)

Meningococcemia is characterized by a hemorrhagic, stellate, often with necrosis in the center, dense rash on an infiltrated basis, which can be of different sizes (petechiae, purpura, ecchymoses) and does not disappear with pressure. In the fulminant form of meningococcemia, purple-black spots may be observed in the lower abdomen and on the inner thighs. The rash appears 1-2 days from the onset of the disease, in the fulminant form - after 2-12 hours, with typical localization on the buttocks, thighs, legs, and sometimes on the torso, upper limbs and face. Secondary elements of rashes have the form of pigmentation. In places of large skin lesions, necrosis is exfoliated to form ulcers, followed by scarring. The following signs should be taken into account in the diagnostic process: very acute onset of the disease, high fever with chills, severe symptoms of intoxication (pale skin, lethargy, adynamia, vomiting, headache, dyspepsia, tachypnea, tachycardia), appearance of meningeal symptoms, signs of endotoxic shock. Similar hemorrhagic rashes may be typical for hemophilic and pneumococcal infection, which causes certain difficulties in differential diagnosis. To confirm the diagnosis, a culture of meningococcus is isolated from the nasopharynx, blood and cerebrospinal fluid;

visual microscopy of blood smear and cerebrospinal fluid («thick drop» of blood and cerebrospinal fluid) and latex agglutination of blood and cerebrospinal fluid (detecting meningococcus antigens) are performed [9, 12, 31].

TYPHOID FEVER AND PARATYPHOID A, B, C

These diseases are characterized by roseolosis rashes, which appear in the 2nd week of the disease in a small amount on the skin of the abdomen and on the lateral surfaces of the chest. Differential diagnostic signs are high body temperature, enlarged spleen, liver, apathy. The disease most often begins with a gradual increase in body temperature to 39 C, an increase in general weakness, malaise, and lethargy. The diagnosis is confirmed by specific methods: bacteriological examination of blood, feces, urine; positive Widal reaction (agglutination reaction) – diagnostic titer 1:200, detection of specific IgM, increase in the titer of specific IgG antibodies over time by ELISA [32].

PSEUDOTUBERCULOSIS AND YERSINIOSIS

These diseases are accompanied by a polymorphic rash and are characterized by the following manifestations: exanthema appears simultaneously on days 3-5 (spotty, papular) with thickening in the area of the palms, soles and back of the head, around large joints; combination of skin rash with arthralgia, enlarged liver, abdominal pain and enteric stools (2-3 times a day); acute onset with high body temperature (38-39 °C); polymorphism of clinical complaints (pain in the abdomen, joints, muscle pain, loose stools); the presence of moderate hyperemia in the oropharynx with symptoms of pharyngitis without plaque on the tonsils and regional lymphadenitis; in the initial period of the disease, the tongue is coated with a gray-white coating, then the inside is cleared and after 3-5 days it takes on the appearance of a «raspberry» tongue; palpation of the abdomen reveals tenderness in the area of the liver and along the mesentery, but mainly in the right iliac region; 10-15% of patients may have symptoms of parenchymal hepatitis (subicteric or icteric skin and sclera, discoloration of urine and feces, hyperbilirubinemia), a short-term increase in the activity of ALT and AST; from 5-6 days, fine bran-like peeling of the skin appears in the torso area and large bran-like peeling on the palms and soles ; lack of effect from treatment with beta-lactam antibiotics within a week; damage to the heart and kidneys. Bacteriological and serological methods are used for diagnosis. The pathogen can be isolated throughout the disease from the feces, urine, bile, sputum, nasopharyngeal mucosa, as well as from the material obtained during surgery. Starting from the 6-7th day of disease, specific antibodies in an agglutination reaction or indirect agglutination reaction with a typical strain or autoculture over time [1, 2, 7].

STAPHYLOCOCCAL INFECTION WITH SCARLET FEVER-LIKE SYNDROME

The clinical picture is characterized by the appearance of small-point («scarlet fever-like») rashes on the hyperemic background of the skin. Exanthema is located on the inner surface of the arms and legs, in the lower abdomen with thickening of the rashes in the natural folds of the skin. The rash appears on the 3-4th day of the onset of a staphylococcal focus of infection, persists for several days. Secondary rash elements in the form of lamellar peeling of the skin appear at 2 or 3 weeks. In the first 2-3 days, the tongue is covered with a white coating, then it is cleaned and becomes «papillary». The following manifestations are typical: acute onset, fever, pronounced symptoms of intoxication, diffuse hyperemia of the oropharynx, sometimes signs of tonsillitis. The presence of a primary septic focus is crucial for diagnosis: an infected wound, panaritium, cellulitis, osteomyelitis, etc. and bacteriological examination [1, 2, 7].

ERYSIPELAS

The following clinical signs are typical for Erysipelas: limited bright hyperemia with clear edges that rise above the skin surface; the boundaries of the lesion are irregular in shape, reminiscent of flame tongues or a geographical map; the tissues around the affected skin are swollen, especially in the area of the face, ears, and legs; sometimes blisters with serous and hemorrhagic contents form at the site of inflammation, which usually open to expose the eroded surface; from the affected area of the skin to the regional lymph nodes (lymphadenitis) there is lymphangitis, which is especially clearly visible during thermographic examination ;the disease begins acutely with chills, an increase in body temperature up to 39-40 C, headache and muscle pain, with the rapid development of local symptoms: pain, burning and a feeling of tension in the affected area. Diagnosis is mainly based on clinical data, electrical thermometry is used (there is an increase in the temperature of erythema compared to areas of healthy skin). Hematological changes in patients with erysipelas are characterized by neutrophilic leukocytosis, toxic granularity of neutrophils, and accelerated ESR. Sometimes a biopsy of the affected area is performed [33].

SECONDARY SYPHILIS

In secondary syphilis, treponema spreads in the body through the lymphatic and blood vessels. As a result, there are various clinical manifestations in the form of localized or diffuse lesions of the skin and mucous membranes (roseola, papules, pustules), generalized lymphadenopathy and damage to internal organs. The main symptom of secondary syphilis is the occurrence of a rash that spreads throughout the body, including the palms and soles. Common signs of rashes in secondary syphilis are the following: lack of subjective sensations (itching, pain); density of elements; dark red color; clear, regular, rounded outlines of elements without a tendency to merge; almost complete absence of peeling of the surface; tendency to spontaneous disappearance without atrophy and scarring. Rashes on the skin and mucous membranes may be accompanied by influenza-like symptoms: headache, body aches, fever. The diagnosis is confirmed by bacterioscopic examination of material from various areas of the affected skin and mucous membranes for treponema, serological examination of blood (Microprecipitation reaction with cardiolipin antigen, Wasserman reaction, sedimentary reactions, group reactions for treponemas, species-specific protein reactions for treponemas, ELISA, indirect hemagglutination reactions, Western blotting (to detect IgG and IgM) and PCR [34].

LYME DISEASE

The leading symptom of Lyme disease is the development of a migrating annular erythema with a primary affect at the site of the bite of an infected tick in the first stage of the disease (in 60-80% of patients). First, a red spot is formed, which spreads over the skin after an average of 10 days and can reach a diameter of 10-15 cm or more. The erythema may be diffuse or appear as a ring with clearing or induration in the center, not rising above the skin level, with a bright red periphery. The erythema is most often localized on the thighs, buttocks, and groin area.. After a few days or weeks, ring-shaped erythema may appear in other places where there were no bites. In some cases, the rash looks like urticaria or diffuse erythema. In addition to annular erythema, the disease is characterized by migrating arthralgias, myalgias, arthritis, damage to the cranial nerves, the nervous system and changes in the heart in the form of ventricular conduction disorders with the development of blockades, myocarditis and pericarditis. In later stages, large joints may be affected. For the purpose of specific diagnosis, IgG and IgM titers are determined by ELISA. At the second stage (in case of a positive (IgG+, IgM+) or doubtful ELISA result) , a western blot is performed to confirm the diagnosis [35].

FELINOSIS (DISEASE FROM CAT SCRATCHES, BENIGN LYMPHORETICULOSIS)

The primary skin changes in felinosis take the form of red, painless papules that often fester and heal without scarring. This disease is also characterized by: slow healing of a wound caused by cat's claws or teeth; regional lymphadenitis (lymph nodes (more often - axillary, less often - cervical and inguinal) increase to 5-10 cm in diameter, are painless; in about 30% of patients, these lymph nodes may melt); fever. The diagnosis in case of suspected disease from cat scratches is confirmed in the presence of the following criteria: anamnestic data on contact with animals (cat scratches, bites, primary skin lesions), sterile pus in enlarged lymph nodes; positive serological reactions, typical histological changes in lymph nodes [36].

PROTOZOAL INFESTATIONS AND HELMINTH INFECTIONS

Cutaneous *leishmaniasis* is characterized by the formation of itchy papules that increase in size, after 3-6 months transform into a painful, crusty ulcer with a granulomatous base (up to 10 mm or more in diameter) and do not heal for a long time. These changes form on exposed parts of the body, at the site of a mosquito bite. After a few months, recovery spontaneously occurs, but a thin depigmented scar remains at the site of the ulcer. Parasites can spread through the lymphatic vessels and affect new areas of the skin, accompanied by tissue swelling and enlarged lymph nodes.

In patients with *ascariasis, enterobiasis, strongyloidiasis, echinococcosis, opisthorchiasis, toxocariasis,* etc., maculopapular (usually allergic) rashes of varying sizes and shapes may appear. Such exanthemas are often accompanied by severe itching. *Trichinosis* is characterized by: swelling of the eyelids, face, diffuse swelling and skin tension, reminiscent of polydermatomyositis; on the skin of the extremities, a maculopapular and hemorrhagic rash occurs; as well as hemorrhages under the nails may be observed. Microscopic (including parasitoscopic) methods and the detection of specific antibodies to pathogens are usually used to diagnose Protozoal infestations and helminth infections.

In typical cases of *scabies*, rashes appear in the form of spots or vesicles, accompanied by significant itching, on the hands, primarily in the interdigital folds. However, modern scabies is accompanied by damage to many other parts of the body, usually with thin skin: the upper extremities (mainly on the curved surfaces), chest, abdomen, inner thighs, legs, etc. Diagnosis is based on the clinical picture, epidemiologic history, identification of paired rashes and scabies passages in

the lesions, microscopic laboratory examination and positive effect of rubbing 5% sulfuric ointment [37-40].

CONCLUSIONS

Thus, as a result of the analysis of existing literature data, it was established that exanthema syndrome is associated with various diseases and pathological conditions, characterized by a variety of clinical manifestations, which requires clinical differential diagnosis and subsequent laboratory confirmation. Comprehensive knowledge of the causes, mechanisms of development, as well as clinical manifestations of skin rash will contribute to the development of an improved algorithm for diagnosis and treatment of diseases accompanied by exanthema syndrome, as well as optimization of therapeutic tactics.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 24.05.2024
ACCEPTED: 09.12.2024