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CLINICAL CASE OF CHEMORESISTANT TUBERCULOSIS IN THE PATIENT WITH TUBEROUS SCLEROSIS: DIFFICULTIES OF DIAGNOSIS, FEATURES OF THE COURSE AND TREATMENT

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Ключевые слова: *химиорезистентный туберкулез, туберозный склероз, факоматоз*

Absract. Clinical case of chemoresistant tuberculosis in the patient with tuberous sclerosis: difficulties of diagnosis, features of the course and treatment. Kolesnik N.S., Marchenko N.A., Stadnik A.I., Ielisieiev V.V., Stepanova T.A. *In the practical activities of a modern doctor, significant difficulties are noted in the diagnostics and proper management of patients with hereditary diseases due to the limited coverage of the population by genetic researches. For a long time, the patients with a variety of complaints are observed by doctors of various specialties, and the therapy often has little effect due to a lack of understanding of the true causes of pathological changes. The situation is complicated by case of a combined course of a hereditarily caused disease and some other disease of an infectious, non-infectious or tumor nature. The aim of the research was to study the characteristics of clinical manifestations, course of tuberculosis with resistance to anti-TB drugs in a patient with a rare hereditary disease from the group of phacomotoses - Bourneville-Pringle disease or tuberous sclerosis. This disease has a wide range of clinical manifestations, accompanied with the development of benign neoplasms in various organs and systems, damages to the skin, brain, organs of vision, lungs, kidneys, heart, as well as the musculoskeletal and endocrine system. It leads to development of various infectious and non-infectious pathologies in these organs. The article covers a 4-year period of observation of a young patient with late diagnosed tuberous sclerosis, suffering from pulmonary tuberculosis and tuberculosis of urinary system, includes the initial diagnosis of a specific disease, the course, the dynamics against received treatment and the development of relapse with the formation of resistance to anti-TB drugs. The difficulties in the management of tuberculosis in this patient were in the detection of numerous neoplasms and changes in the internal organs, in particular in the kidneys and lungs, which characterized tuberous sclerosis, on the one hand this contributed to untimely diagnosis of tuberculosis, and on the other hand – worsening the course and the progression of a specific process, as well as an unfavourable prognosis for recovery.*

Реферат. Клинический случай химиорезистентного туберкулеза у больной с туберозным склерозом: трудности диагностики, особенности течения и лечения. Колесник Н.С., Марченко Н.А., Стадник А.И., Елисеев В.В., Степанова Т.А. *В практической деятельности современного врача отмечаются значительные сложности в диагностике и правильном ведении пациентов с наследственными заболеваниями в связи с ограниченным охватом населения генетическими исследованиями. В течение длительного времени пациенты*

наблюдаются с разнообразными жалобами у врачей различных специальностей, а проводимая терапия зачастую является мало результативной из-за непонимания истинных причин патологических изменений. Ситуация осложняется в случае сочетанного течения наследственно-обусловленного заболевания и какого-либо другого заболевания инфекционной, неинфекционной либо опухолевой природы. Целью исследования явилось изучение особенностей клинических проявлений, течения туберкулеза с лекарственной устойчивостью к противотуберкулезным препаратам у пациентки с редким наследственным заболеванием из группы факоматозов – болезни Бурневилля-Прингла, или туберозным склерозом. Это заболевание с широким спектром клинических проявлений, сопровождающееся развитием доброкачественных новообразований в различных органах и системах, поражением кожи, головного мозга, органов зрения, легких, почек, сердца, а также опорно-двигательного аппарата и эндокринной системы, что нередко является фактором риска для развития в них различных инфекционных и неинфекционных патологий. Представленный в статье случай охватывает 4-летний период наблюдения за молодой пациенткой, с поздно диагностированным туберозным склерозом, страдающей туберкулезом легких и мочевыделительной системы, включая первичную диагностику специфического заболевания, особенности течения, динамику на фоне проводимого лечения и развития рецидива с формированием резистентности к противотуберкулезным препаратам. Сложность в ведении туберкулеза у данной пациентки заключались в обнаружении многочисленных новообразований и изменений во внутренних органах, в частности, в почках и в легких, характерных для туберозного склероза, что способствовало, с одной стороны, несвоевременной диагностике туберкулеза, а с другой - ухудшению течения и прогрессированию специфического процесса, а также неблагоприятному прогнозу для выздоровления.

Tuberous sclerosis is a hereditary autosomal-dominant disease that is determined by mutations in the TSC1 genes of the 9th chromosome in the 9q34 region, and in the TSC2 of the 16th chromosome in the 16p13 region, which are natural tumor-suppressor genes. It is characterized by the formation of hamartomas in different organs and systems due to hyperplasia of derivatives of ecto- and mesoderm. In the patients lesions of the skin, nervous system, visual organs, kidneys, lungs, heart, musculoskeletal system, endocrine system are noted.

History. The disease was first described by the German pathologist F. von Recklinghausen in 1862. The term "tuberous sclerosis" was used by the French neurologist D. Bourneville in 1880 [7].

Epidemiology. The incidence of tuberous sclerosis is 1 case per 20 000 people. Prevalence among newborns is from 1:6000 to 1:10 000 [1,3,5,12].

Clinical manifestations and diagnostics. The manifestations of tuberous sclerosis are diverse. So, skin manifestations in patients have several variations. More common are angiofibromas and fibromatous foci on the face, trunk, areas of "shagreen" skin, formation of the nail and surrounding nails. In 90% of patients hypomelanotic spots are diagnosed since birth, which are often the earliest symptomatic manifestation of the disease [7]. The number of spots with age may increase.

“Shagreen” skin (peau chargin, translated from French as "rawhide, rigid, rough skin") is a mandatory sign of tuberous sclerosis, which is observed in 21-68% of cases and appears in the second decade of the patient's life. On the affected areas, more often in the lumbar spine, plaque-like formations of dense consistency, yellowish-brown or pink are detected.

Facial angiofibromas are observed in 45-90% of patients with tuberous sclerosis [5, 7]. They occur mainly at the age of 4-10 years and have the appearance of symmetrically placed globular tumor elements, usually in the area of the nasolabial wrinkles, wings of nose and cheeks (“butterfly wings”), chin. The formations are characterized by a smooth, radiant surface of dense consistency, ranging in size from 2 to 5 mm.

Paraungual and subungual fibromas (Kenen tumors) occur in the second decade of life in 17-52% of patients [6, 7]. Papules or nodes of red color are formed from the nailbed or around the nail plate. Most often they occur on the lower extremities in women.

In 30% of patients with tuberous sclerosis, fibromas pendulum are observed, with the most frequent localization on the neck, as well as the extremities and trunk. In addition to fibromas, other benign tumors such as lipomas, pigmented nevuses may develop.

In 80-92% of patients with tuberous sclerosis already in the newborn period convulsive paroxysm occurs, which is a manifestation of central nervous system injury. This symptom further progresses to epileptic seizures, mental retardation development, mental deficiency, and behaviorial disorders. Clinical brain lesions develop as a result of intracerebral calcification (formation of tubers) or development of giant-cellular astrocytes, white matter abnormalities. In convulsions related directly to tuberous sclerosis, resistance to standard anticonvulsant therapy has been observed [7,11,12].

Oftentimes there are lesions of visual organs in the form of phacomas, hamartomas of retina with

signs of calcification, formation of depigmented areas on the retina and / or iris, angioid strips, which leads to a progressive reduction in vision, development of nystagmus.

On the part of the cardiovascular system the pathology manifests itself in the form of development of rhabdomyoma of the heart. Most of them with the age of the patient are resolved spontaneously or reduced in size. Ultrasound diagnostics makes it possible to detect tumors of the myocardium as early as during the prenatal development of the fetus, starting from the 21st week of pregnancy.

Damage to the liver and kidneys is manifested by the development of cysts, fibroadenomas, angiolipomas. On examination hamartomas in the large intestine are often revealed. Foci of lesions can also be found in the osseous-articular system, where radiographically foci of sclerosis, pseudocystic changes are detected.

In lesions of the bronchi-pulmonary system cysts and lymphangiomas are often found [5,12]. X-ray examination of the chest cavity can detect pathological changes in the form of "cellular lung", miliary insemination. Clinical manifestations of respiratory damage may be shortness of breath, hemoptysis, pneumothorax.

Diagnosis of tuberous sclerosis. When examining patients, the multi-organism of the lesion should be taken into account. Computed tomography of the brain, chest and abdominal organs, ultrasound diagnosis of liver, kidney, electrocardiography, echocardiography, ophthalmoscopy, as well as histological examination of pathological material and genetic testing are used [7, 8, 10, 12].

Treatment includes pathogenetic and symptomatic therapy. [2, 4, 5, 12]. Patients often need individual care due to the development and aggravation of mental retardation, seizures.

The prognosis for recovery is unfavorable. Mortality is caused by changes in the brain, the development of chronic renal failure, multiple organ lesions. 30% of patients do not reach the age of 5 years (in severe course), about 50% of patients die in childhood and adolescence [5, 7, 8].

Considering the presence of burdened premorbid condition of patients with tuberous sclerosis, as well as multiple organ lesions, patients often develop concomitant pathologies, infectious diseases overlay. This article describes a clinical case of generalized tuberculosis caused by resistant strains of mycobacteria in a patient with tubercle sclerosis.

The aim is to demonstrate the difficulties of diagnosing and managing the clinical case of multidrug-resistant tuberculosis (MRTB) in a patient with tuberous sclerosis.

MATERIALS AND METHODS OF RESEARCH

Patient Ya., aged 32, sought medical advice from the Municipal enterprise «Dnipropetrovsk Clinical Treatment and Prophylactic Association «Phthisiatry» of Dnepropetrovsk Regional Council» (ME «DCTPA «Phthisiatry» DRC») with complaints of girdling pain in the lower back, fever up to 37.4-37.7^0 C for 3 weeks, decreased appetite, weight loss up to 3 kilograms in 3 weeks, general weakness.

From the anamnesis it is known that at the age of 7 the patient sought medical advice from physicians at the skin and venereological dispensary for the correction of a cosmetic defect in the form of a pigmentary nevus in the area of the supraorbital ridge. According to the patient, she underwent several procedures for cryodestruction of this formation, but the positive effect of treatment was not achieved. In parallel, patient was treated for a tentative diagnosis of onychomycosis, as there were lesions of the nail plates on the upper and lower extremities. However, the therapy performed had no effect. After several years of follow-up at the skin and venereological dispensary and the absence of positive dynamics, the patient refused medical treatment.

It is known that the patient noted a decrease in the level of performance and poor assimilation of school material, poor learning ability.

In the 2000 s, the patient again referred to the skin and venereological dispensary at the place of residence with complaints of "facial rash". After examination, patient was diagnosed with demodicosis and treatment was started, but the effect was not observed, so the patient again refused the proposed follow-up.

In July 2013, the patient had complaints of fever up to 37.7°C for 3 weeks, decreased appetite, weight loss up to 3 kilograms in 3 weeks, general weakness, girdle pain in the lower back, more on the right.

On further examination at the outpatient stage, as well as in the department of extrapulmonary forms of tuberculosis in the tuberculosis institution, the following was revealed: according to ultrasound diagnostics of abdominal organs, the presence of multiple renal angiolipoma on the background of phacomatosis, chronic pyelonephritis, phase of unstable remission. The diagnosis of chronic renal failure was additionally established.

General analysis of urine (31.05. 2013): color – yellow, specific gravity – 1012 g/ml, pH – 5.0, leukocytes – 1-3 in vision field, scaly epithelium –

1-2 in vision field, erythrocytes – not detected, protein – not detected.

Zymnitsky's test (01.06.2013): daily diuresis – 900 ml, night diuresis – 890 ml, diurnal diuresis – 1790 ml, specific gravity – 1006 g/liter.

Nechiporenko's test (01.06.2013): leukocytes – 2500 in 1 ml, cylinders – 8 in 1 ml, erythrocytes – not detected.

During the radiographic examination of the chest organs (01.06.2013), no pathology was detected.

Given the lack of convincing data on the tuberculosis process, the patient was discharged from the ward for further outpatient follow-up until the results of the urine test for mycobacterium tuberculosis by bacteriological method were achieved. On outpatient follow-up the above complaints remained unchanged.

After confirming the presence of mycobacterium tuberculosis by bacteriological method in the urine, the following diagnosis was made: first diagnosed tuberculosis (FDTB) (24.07.2013) of the kidneys (parenchymal) destruction (Destr) - mycobacterium tuberculosis (MBT) + microscopic examination (microscopic examination) (M) – culture study (K) + tuberculosis resistance (Resist) 0 histological examination (Hist) 0 Category (Cat) 1 Cohort (Coh) 3 (2013). Chronic renal failure, 0 st. Chronic cholecystopancreatitis. The patient was hospitalized to extrapulmonary unit of ME «DCTPA «Phthisiatry» DRC», where she received 2 months' treatment according to the standard scheme: isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 2000 mg and ethambutol 1600 mg. at a daily dose. After inpatient treatment, she was discharged for outpatient treatment with two drugs: isoniazid 300 mg and rifampicin 600 mg for 4 months at a daily dose.

In November 2014, the patient again referred to the consulting clinic of the medical center «DCTPA «Phthisiatry» DRC» with complaints of girdling pain in the lower back, fever to 37,4-37,7^{o} C for 3 weeks, decreased appetite, loss of weight up to 3 kilograms in 3 weeks, general weakness. Ultrasound examination of abdominal organs (11/04/2014): left kidney – 103x54 mm, preserved parenchyma, ectasia of the pelvicaliceal system – not detected, calcified formations of 18x24 mm were determined; the right kidney – 100x57 mm, induration of the parenchyma, calcinates.

Cystoscopy (11.05.2014): mucous membrane of pale pink color, vascular pattern moderately expressed. Ureter orifices are slit-like. Small area of hyperemia, 0.5 mm in size.

Chest X-ray examination (04.11.2014): no lung pathology detected.

Common urine analysis (19.11.2014): color – yellow, specific gravity – 1016 g/ml, pH – 5.2, leukocytes – 1-3 in vision field, scaly epithelium – 2-3 in vision field, erythrocytes – not detected, protein – not detected.

Clinical diagnosis was established: Treatment failure (TF) (07.11.2014) of the right kidney (papillitis), urinary bladder (infiltrative) Destr + MBT - M - K0 Resist 0 Hist.0 Cat 2 Coh 4 (2014). Chronic renal failure, 0 st. Chronic cholecystopancreatitis.

The patient was hospitalized to extrapulmonary unit of «DCTPA «Phthisiatry» DRC» where she was treated for 2 months according to the standard scheme: isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 2000 mg and ethambutol 1600 mg every day. After completing a complete course of antituberculosis therapy, improving the general condition and stabilizing the process in the kidney, the patient was transferred to category 5.1, and outpatient follow-up at the place of residence was started.

In April 2016, the patient referred to «DCTPA «Phthisiatry» DOR» with complaints of girdling pain in the lower back, more on the right, fever to 37.4-37.9^{o}C during the last month, decreased appetite, general weakness, cough with mild discharge of mucoid sputum, shortness of breath during exercise, feeling of heaviness in the chest area on the right. The patient was hospitalized. According to the results of computed tomography of the chest and abdominal organs: in the lungs – diffuse lesions of parenchyma due to numerous cysts (0.5-1.2 cm) with thin walls up to 1 mm. In the lower part of the sixth segment of the left lung – the areas of decrease in pneumatization by the type of frosted glass, up to 15x30 mm (Fig. 1). Kidney: right kidney 196x112 mm, left – 172x95 mm, parenchyma diffusely subtotally is replaced by fat component, presented in the form of multiple formless fragments (kidney angiolipomatosis). Pelvicaliceal system is dilated, deformed, ureters are pathologically twisted (more on the right). In the left lobe of the liver – small cysts of up to 3-7 mm (Fig. 2).

Multiple cystic lesions of white and gray matter were detected in brain imaging (Fig. 3).

Common urine analysis (05.04.2016): Color - straw yellow, specific gravity – 1012 g/ml, pH – 5.0, leukocytes – 1-3 in visual field, scaly epithelium – 2-3 in visual field, erythrocytes – not detected, protein – not detected.

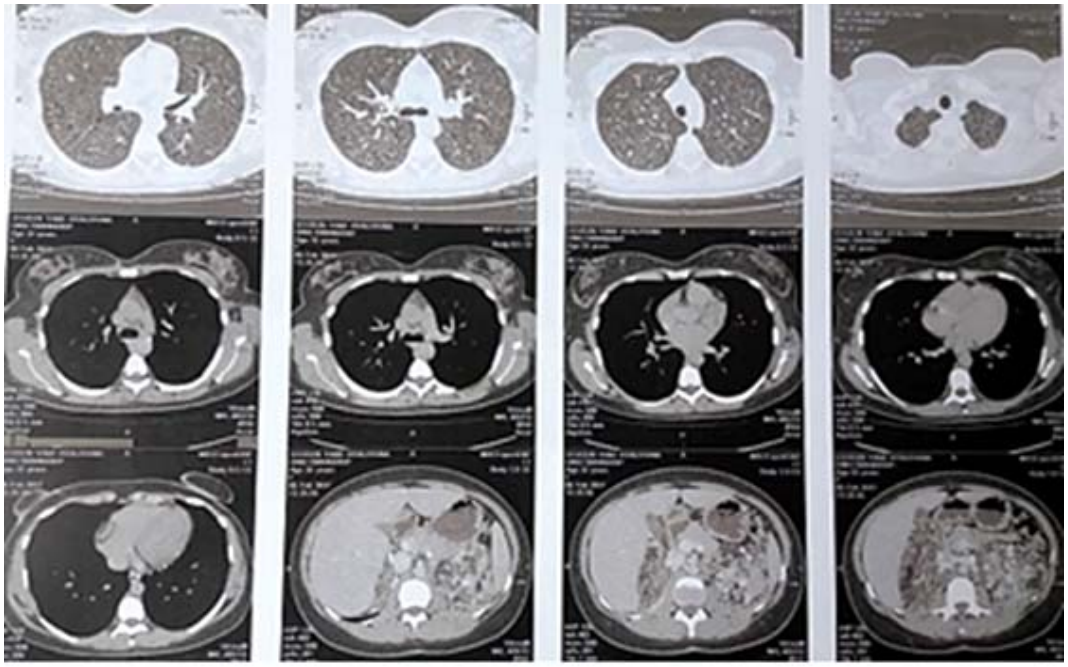

Fig. 1. Diffuse lesion of the parenchyma due to numerous cysts is in the lungs. In the sixth segment of the left lung areas of reduction of pneumatization by the type of frosted glass are defined

In the study of sputum by bacterioscopic and bacteriological methods MBT were not detected, however, in the study of sputum by molecular-genetic method (Gene Xpert) the causative agent of tuberculosis and its resistance to the main anti-tuberculous drug – rifampicin was determined. Based on the results of the further examination the patient was diagnosed with: Rifampicin-resistant tuberculosis (RifTB) (07.04.2016) lungs (miliary), kidneys (papillitis), bladder (infiltrative) Destr - MBT + M - molecular genetic study (MG) + rifampicin resistance (Rif) + K 0 Resist 0 Hist 0 Cat 4 Coh 2 (2016). Chronic renal failure, 0 st. Chronic cholecystopancreatitis. The following drugs were prescribed: pyrazinamide 300 mg, kanamycin 1000 mg, levofloxacin 750 mg, cycloserine 750 mg, protamide 750 mg per day.

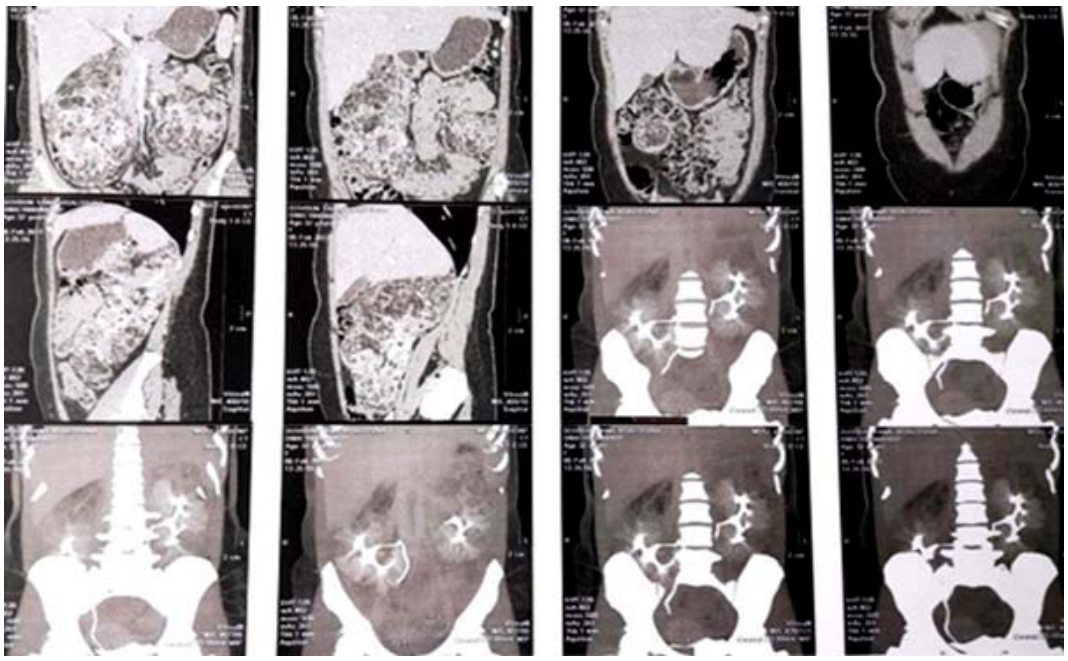

Fig. 2. Multiple formless fragments are identified in the kidneys. Pelvi-caliceal system is enlarged, deformed, ureters are pathologically twisted (more on the right). In the left lobe of the liver small cysts of up to 3-7 mm are identified

The patient was treated in the extrapulmonary unit for 4 months, after which she was transferred for outpatient treatment due to improvement of the general condition and stabilization of the pulmonary and renal tuberculosis process.

On January 23, 2017, the patient was again hospitalized with complaints of girdling pain in the lower back region, fever up to 37.6° C for 2 weeks, decreased appetite, general weakness, cough with mild discharge of mucoid sputum, shortness of breath during excercise. A general examination revealed rash in the area of the wings of the nose, cheeks. On the skin of the lower back several plaque-like formations of the type "orange peel" of yellowish-brown were determined. Nail plate lesions were also observed (Fig. 4). Several convulsive paroxysms were recorded during the hospital stay.

The patient was referred to a skin and venereological dispensary of Dnipro city for further examination. Biopsy of the damaged area of the wings of the nose was performed. Histopathological examination of the biopsy specimen revealed connective tissue accrementition and proliferation of small vessels. On 27.01.2017 on the basis of the following symptoms and histological examination of facial angiofibroma the diagnosis of "tuberous sclerosis" was established: single seizure attacks, signs of organic brain damage, characteristic manifestations on the skin (angiofibromas of the face, areas of "shagreen" skin, periungual fibromas, areas of skin depigmentation) pathology of inner organs,. Symptomatic treatment was prescribed.

On bacteriological examination of the sputum from 23.01.2017, myocardial tuberculosis, which already had MBT resistance to isoniazid, rifampicin and streptomycin was detected.

The diagnosis was made on the basis of laboratory and radiological methods of examination of the patient: MRTB (27.01.2017) lungs (miliary), kidney (papillitis), urinary bladder (infiltrative) Destr - MBT + M - MG + Rif + K + resist + (isoniazid, rifampicin , streptomycin) Hist 0 Cat 4 Coh 1 (2017). Tuberous sclerosis. Chronic renal failure, 0 st. Chronic cholecystopancreatitis.

RESULTS AND DISCUSSION

On radiological examination on June 19, 2017, a total lesion of the lung tissue with foci from 2 to 10 mm in size was observed. Despite anti-tuberculosis therapy, radiographic dynamics is poorly positive, this may be due to the presence in the lungs of both tuberculous and lesions specifically attributed to tuberous sclerosis together.

Thus, tuberous sclerosis has significant difficulties in the diagnosis and management, and concomitant pathology in these patients has poor expected response to treatment.

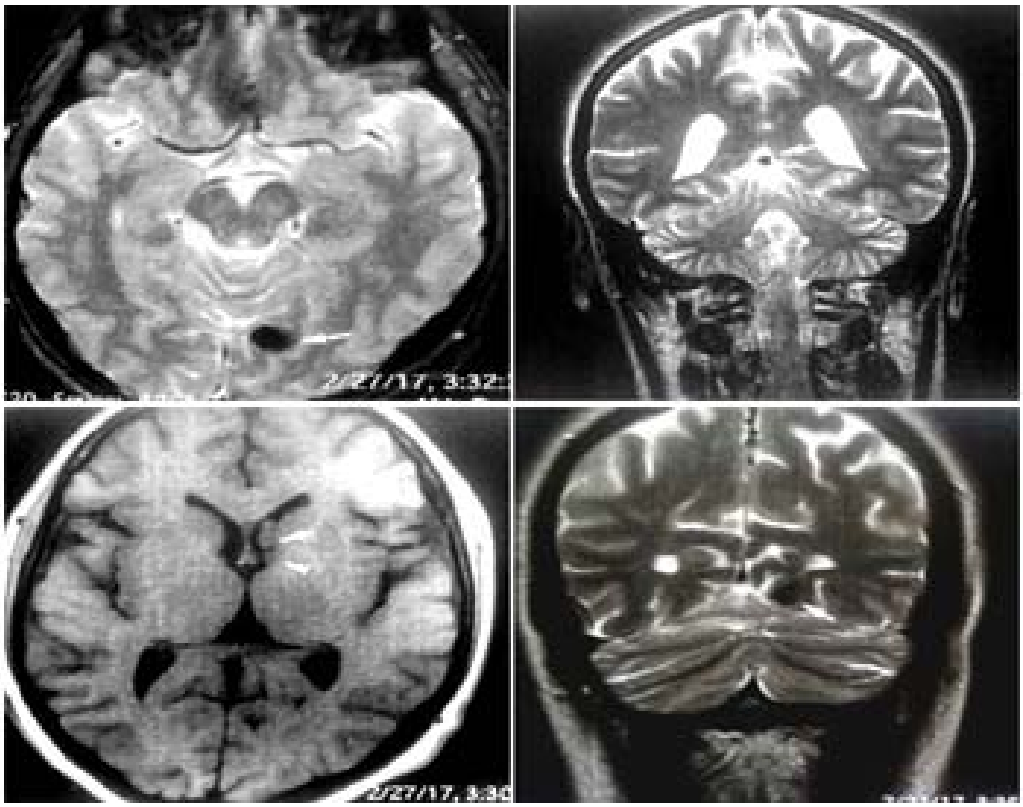

Fig. 3. Multiple cystic lesions of white and gray brain matter

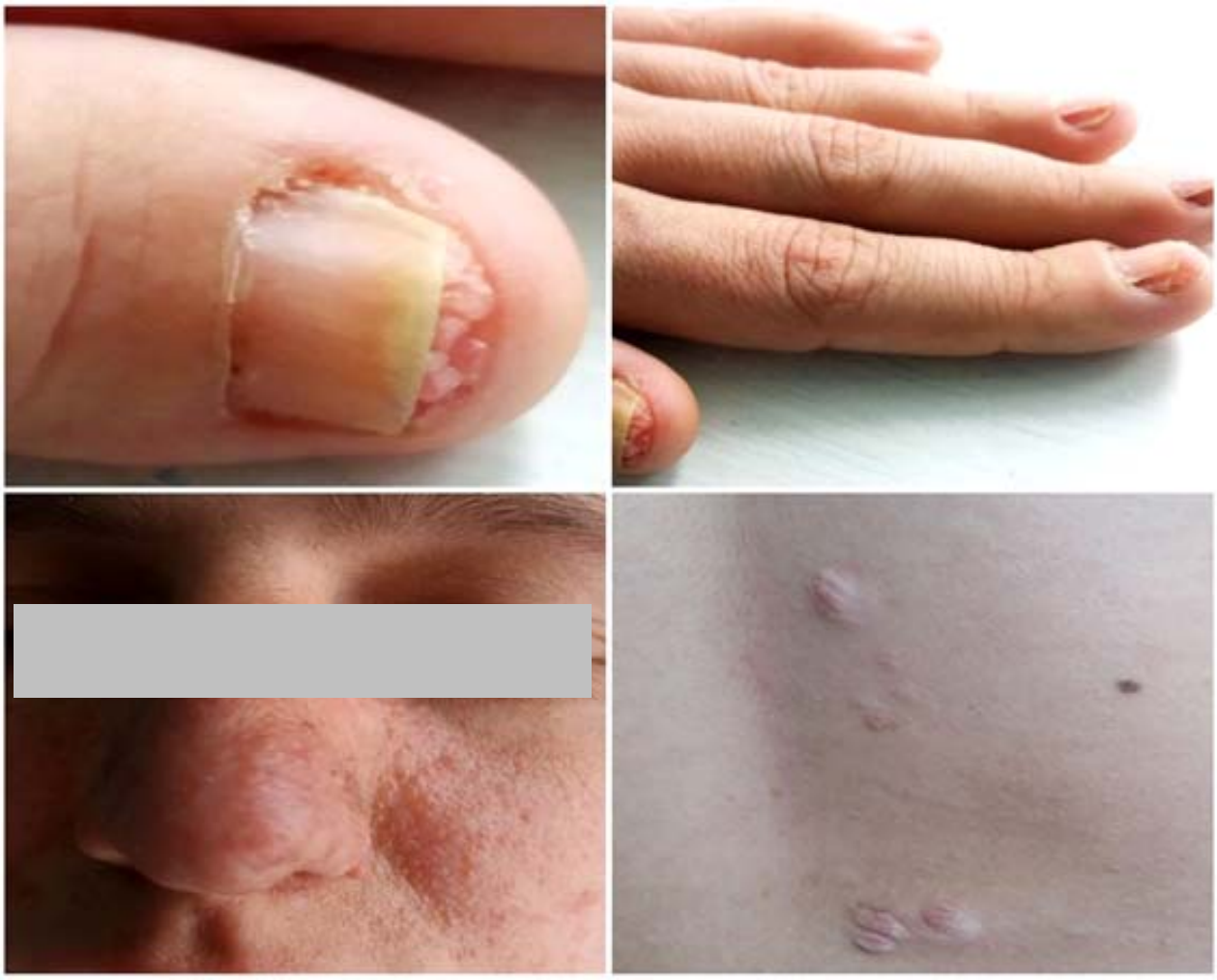

Fig. 4. Rash in the area of the wings of the nose, cheeks, on the skin of the back - plaque-like formation, damage to the nail plate

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