Difficulties in rare diseases diagnostics: a clinical case of Weber-Christian disease.

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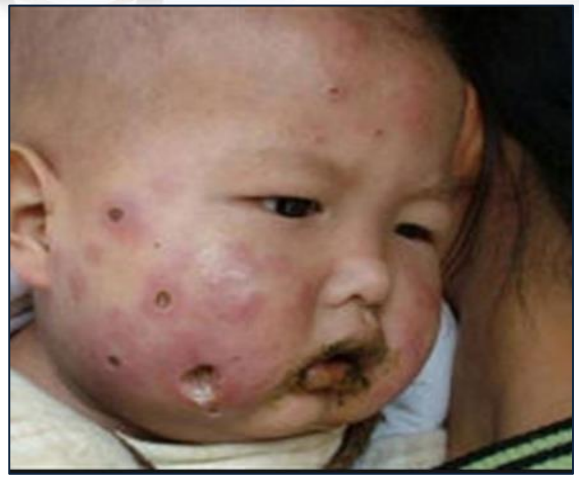
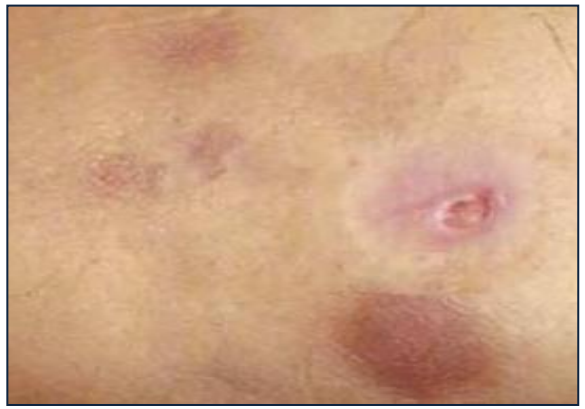
Introduction

- A rare disease Defined by the European Union as one that affects less than 5 in 10,000 of the general population. Around 7000 known rare diseases and around five new rare diseases are described each week.
- 80% of rare diseases have a genetic component. Often rare diseases are chronic and life-threatening.
- **Panniculitis** – group of heterogeneous inflammatory diseases, characterized by lesions of subcutaneous fat layer of the skin with involvement in the process of musculoskeletal system and internal organs.
- **Weber-Christian disease (WCD)** is a rare disease from the group of panniculitis, characterized by subcutaneous nodules, inflammatory cells in the fat lobules, and systemic symptoms.

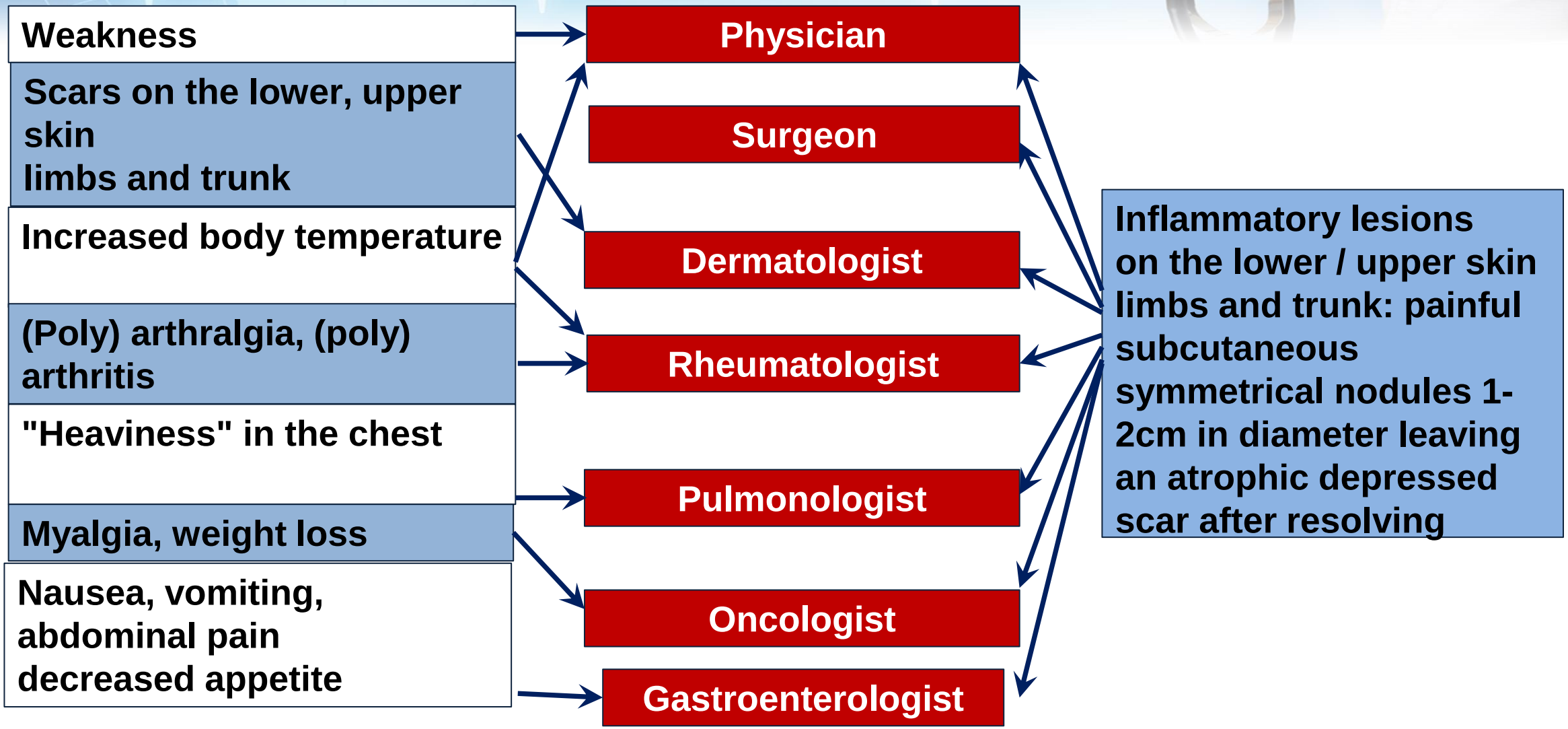




https://www.raredisease.org.uk/what-is-a-rare-disease/

http://www.kbs-frb.be/uploadedImages/KBS-FRB/Files/Kaft_-_Logo/rare%20diseases.jpg

Referral to various specialists in WCD



Adopted from: “Панникулиты в практике ревматолога-Б.С. Белов, О.Н. Егорова, С.Г. Раденска-Лоповок- Науч-практич ревматол 2013; 51(4): 407-415”

Our patient

- Name: B.G.M.
- Sex: Female.
- Age: 57 Years.
- Location: Kharkiv.
- Occupation: Not working.

Complaints:

- The patient complains of a burning sensation and tightness of the skin in the area of the anterior abdominal wall, loin, hips; pain in the cervical, thoracic, lumbar regions of spine, joints of wrists, feet, knees with the mechanical rhythm of pain and morning stiffness for about 15 minutes, “crepitus" in the joints during movement and restriction of its motion; torso muscle pain.
- Also complains of recurrent headaches of diffuse nature, dizziness, fatigue, general weakness, periodical chest pain without irradiation provoked by stress, relieved in rest.
- Patients is concerned about progressive memory loss, periodical chills, feeling of a lump in the throat, difficulty in swallowing.

Anamnesis of present illness

From early childhood, the patient has acquired skin defects (extensive scarring), presumably due to past infectious lesions of the skin in the early neonatal period (in the age of 4 days). In 2008 after surgery for uterine leiomyoma, the patient began to notice the appearance of a feeling of skin tightness in the area of these lesions, muscle aches, joint pain, aching, diffuse abdominal pain, periodical increase of temperature up to 37, 2C. However, since 2012 the patient's condition began to deteriorate progressively - the feeling of skin tightness has intensified, appeared painful nodules with bluish-purple staining of the skin with fluctuation over it in the area of the front wall of the abdomen, loin, hips; memory worsened significantly, appeared pain in the area of thyroid gland projection, dizziness. The patient referred to the endocrinologist, neurologist, dermatologist and was sent for consultation to the genetic center, where Werner syndrome was suspected.

In 2013, she was consulted by rheumatologist and directed to the rheumatology department of Kharkiv City Hospital №28, where she was diagnosed with primary recurrent spontaneous nonsuppurative panniculitis (Weber-Christian disease); she was treated with corticosteroids and NSAIDs with positive dynamics of her state – decreased temperature, diminished pain and skin changes. Subsequently, the patient is held annually examinations and treatment in a specialized rheumatology department.

Anamnesis of life

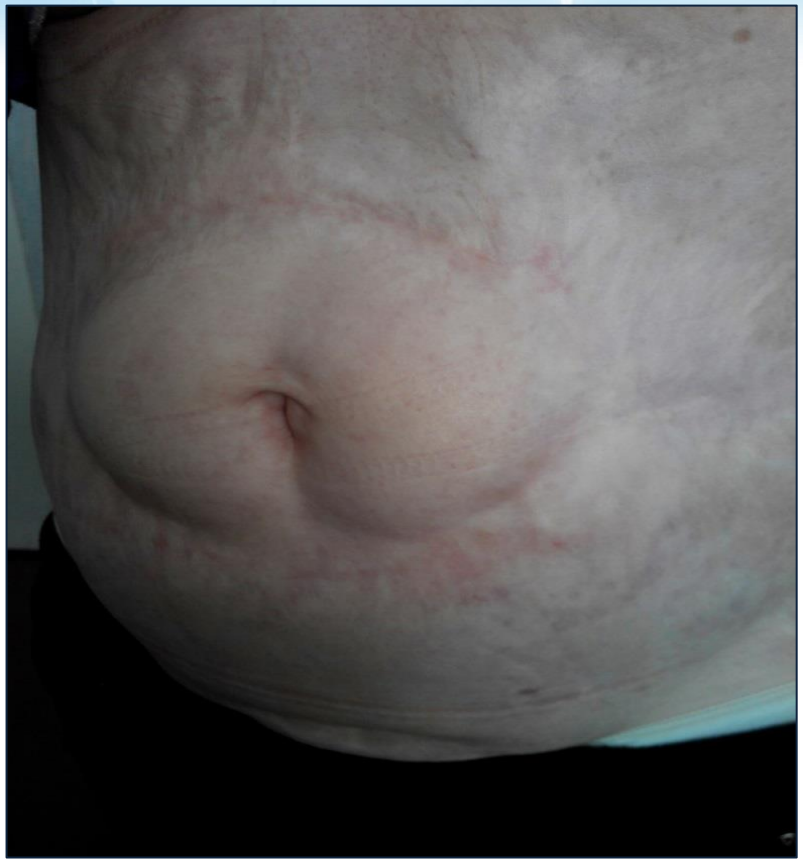
- Patient is not working ,denies smoking, alcohol abuse;
- Menopause since 2008 (surgical menopause - hysterectomy, ovarectomy);
- According to the patient 30 yrs ago she was first diagnosed with autoimmune thyroiditis, hypothyroidism; constantly takes L-thyroxin (75-100mg)
- First was diagnosed with high blood pressure 7 years ago, constantly takes antihypertensive drugs (lisinopril);
- 16.Jul.2015- ischemic stroke in the basin of the left middle cerebral artery with right-sided hemiparesis – inpatient treatment (IT)– hospital #4.
- Apr 2016 –inpatient treatment with open-angle glaucoma 1a st, retinal angiopathy of both eyes of hypertensive type;
- June 2016 – surgery – inflamed right upper jaw granulomas in the area of 14,16, 17 teeth

Objective status

- Height - 162cm, weight - 76 kg, BMI = 29kg / m2
- Skin: pale with areas of vitiligo; slightly dry, skin turgor preserved; on the front of the abdominal wall - skin atrophy with elements of scarring and slight cyanosis; in the right thigh - skin scarring with purple-bluish coloration, slightly painful on palpation.
- Visible mucous membranes are clean, moist; subcutaneous adipose tissue is developed moderately, distributed symmetrically.
- Musculo-skeletal system: the outline of small joints of the hands, wrist, knee, ankle, foot joints is smoothed . There are solitary Heberden nodes in the DIP and Bouchard nodes in the PIP of the hands; in the 1st MTP joints of the feet – signs of exostosis. On palpation joints are painless, with crepitus on motion.
- Thyroid gland is not enlarged;
- Lungs: resonance percussion sound, vesicular breathing over the lungs fields, RR-19/'
- Heart borders extended to the left on 1 cm, heart tones are rhythmic, clear with HR 72 bpm. BP *sin* 160/100 mm Hg, *dext* 160/102 mm Hg, radial pulse is synchronous, rhythmic at 72 bpm.
- Abdomen: abdomen is painless on superficial and deep palpation in all regions. Liver at the costal margin, painless; spleen is not palpable. Pasternatskiy sign is negative on both sides. Urination is free, painless.

Objective status

1



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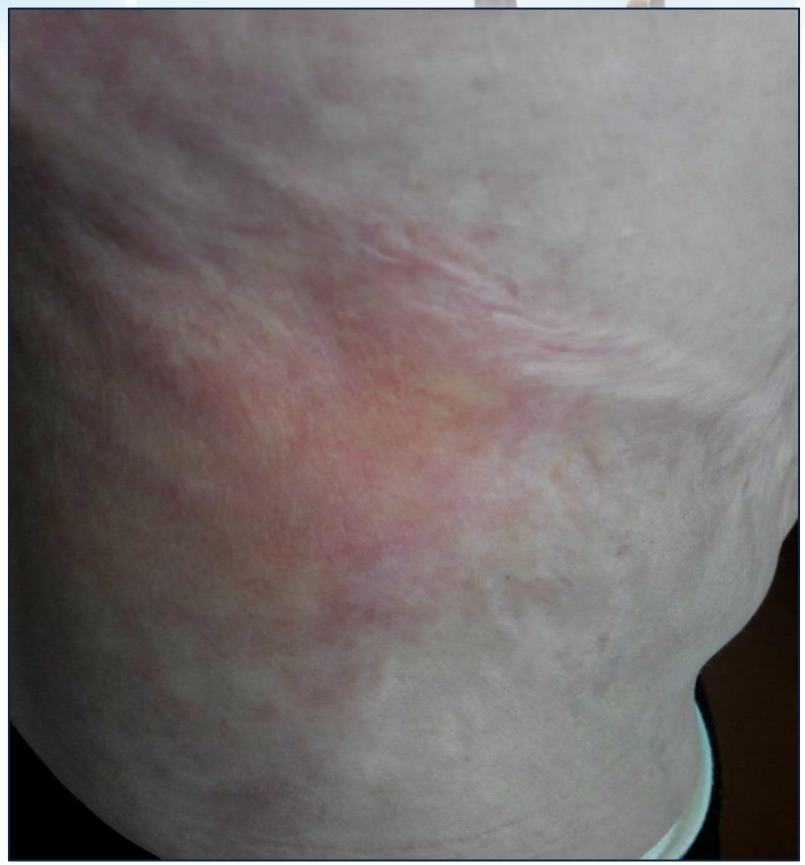


Pic 1. On the front of the abdominal wall - skin atrophy with elements of scarring and slight cyanosis;

Pic 2. On the loin - skin scarring with purple-bluish color, slightly painful on palpation.

Data of additional tests (I)

- Full blood count – leucocytosis: 9,5*10^9/L, increased ESR: 20mm/h, eosinophilia: 7%;
- Urinalysis - all parameters within the normal range
- Biochemical panel - decreased ionised Ca: 1,0mmol/l;
- Thyroid function tests - all parameters within the normal range
- Ultrasound of thyroid gland - not enlarged, diffuse-focal pathological changes of thyroid gland
- ECG - sinus rhythm with HR 74 bpm, non-specific ST-T changes in left ventricular posterior wall
- EchoCG : Sclerotic changes in the walls of the aorta, signs of left ventricular hypertrophy.

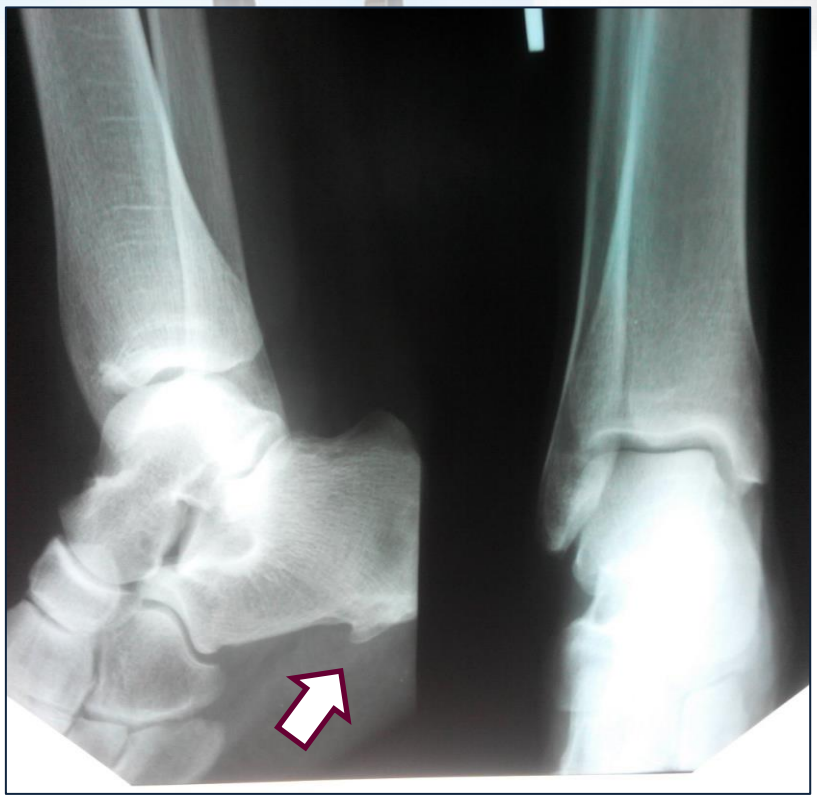
Data of additional tests (II)

Options	Results	Notes
ANA (Anti-nuclear antibody)	positive	is common in most autoimmune diseases with high sensitivity but lacks specificity; also may be found in nonrheumatic autoimmune diseases, in various infections and malignancies.
RF (Rheumatoid factor)	negative	sensitive, specific for RA (70%), also may be seen in SLE, Sjogren's syndrome, etc. ~15% of the healthy population may have a low titer RF.
anti-ENA (Anti-extractable nuclear antigen)	negative	Consist of the Smith (Sm) antigen (highly specific for SLE), ribonuclear protein (RNP) or U1RNP (SLE plus systemic sclerosis), anti-SSA (Ro) and anti-SSB (La) (Sjögren's syndrome and may be seen in SLE).
anti-dsDNA (Anti-double stranded DNA)	positive 40	highly specific for SLE, however, some patients with other rheumatic diseases or chronic active hepatitis may have mildly or moderately elevated serum titers
anti-JO-1	negative	high specificity to the polymyositis, dermatomyositis
Anti-Chromatin	negative	Renal disease, drug-induced lupus
Anti-Scl70,Anti-Centromere	negative	specificity to systemic sclerosis

Data of additional tests (III)

- Chest X-ray: without pathological changes;
- X-ray of wrists, feet: signs of polyosteoarthritis
- MRI of spine - polysegmental vertebral osteochondrosis, spondylarthritis, spondylosis, disc protrusions at the level L3-L4, L5-S1.
- Densitometry of forearm – mineral density in distal region is decreased, osteopenia, T-score: –1,8;
- Densitometry of spine - mineral density of L1, L2, L3, L4 is decreased – significant osteopenia, total T score: - 2,4.

Normal mineral density	T-score less than -1,0
Osteopenia	T-score between -1,0 and —2,5
Osteoporosis	T-score is -2,5 and below



Pic3. X-ray of left foot: assymetric narrowing of the interarticular space; subhondral sclerosis, presence of osteophytes

Diagnostic criteria of WCD

Due to Ukrainian Association of rheumatologists diagnostic criteria for WCD are:

Clinical criteria	The acute (subacute) forming of moderately painful nodes in subcutaneous fat (solitary or conglomerates), mainly in the area of the torso, thighs, forearms.
	High or low-grade fever preceding the appearance of nodules
	Polyarthralgias
Laboratory criteria	Increased ESR, leucocytosis, eosinophilia
Histological criteria	Edema, foci of necrosis of fat lobules
	Cell infiltration with lymphocytes, plasma cells, histiocytes

Course of disease: acute, subacute, chronic;

Activity: 0 (absent), 1 (minimal), 2 (moderate), 3 (high).

Clinical forms of WCD:

1. **Nodular** – nodules clearly demarcated from the surrounding tissue with normal skin color to bright pink.
2. **Plaque** – nodules are merged in a dense lumpy conglomerate, color over it varies from pink to bluish-purple.
3. **Infiltrative** - fluctuations in the area of separate lesions or conglomerates with red, purple or bluish-purple color.

Diagnosis of the patient

- **Main:** **Reccurent lobular nonsuppurative panniculitis (Weber-Christian disease), chronic course, activity of 1 st., with primary subcutaneous fat tissue lesion (infiltrative form). Primary polyosteoarthritis with lesions of small joints of wrists, wrist, ankle, knee, small joints of the feet. Spondyloarthritis. Insufficiency of the joint function I degree, Ro I. Osteopenia.**
- *No conclusive data indicating the presence of Werner syndrome in our patient*.
- **Concomitant diagnosis: Osteochondrosis with a lesion of the lumbo-sacral spine. Polysegmetal unstable form. Instability of the vertebral-motor segments of L3-L4, L4-L5, L5-S1, herniated intervertebral disks of L4-L5, L5-S1.**

  Chronic autoimmune thyroiditis, diffuse-nodular form. Hypothyroidism, severe form, compensatory stage.

  Arterial hypertension stage III (ischemic stroke 2015), grade 2. Retinal angiopathy of both eyes of hypertensive type, open-angle glaucoma of both eyes 1a degree.

  Ischemic heart disease. Atherosclerotic cardiosclerosis.

  CHF, stage IIa, with preserved left ventricular pump function (EF- 62%), III FC (NYHA).

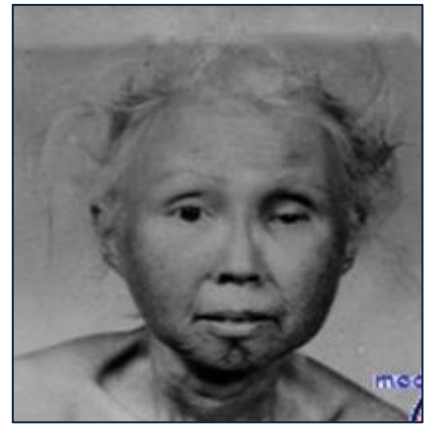
  CV Risk 4.

Treatment and recommendations

- Recommendations to maintain healthy lifestyle, decrease sodium intake, lipid lowering diet, aerobic non strenuous exercises;
- Meloxicam 15mg per day - 10 days, and in the subsequent course of no more than 10 days in the event of pain
- Hydroxychloroquine (plakvinil) 0.2 g 2 time per day for a long time
- Glucosamine sulfate 1500mg per day for 3 months, after 6 months a second course may be given.
- Osteogenon (combined formulation with calcium and phosphorus) 2 tab twice daily for 6 months under the control of serum calcium and phosphorus
- Zolopent (pantoprazole), 40 mg once daily for 7 days
- L-thyroxin 100mg per day under control of thyroid hormones;
- Bisoprolol 5mg in the morning, lisinopril 10mg in the evening under blood pressure control;
- Aspirin 75mg once daily continuously;
- Repeat densitometry after 6 months, autoantibodies after 3 months;
- Repeat visit to rheumatologist, endocrinologist, neurologist after 3 months.

Criteria for the diagnosis of Werner s-me

WS (progeria of adults) is autosomal-recessive disease caused by the mutations at the *WRN* gene locus on chromosome 8



Criteria by International Registry of Werner's syndrome group:

4 cardinal signs:

- ❑ Bilateral ocular cataracts (present in 99%)
- ❑ **Premature graying and/or thinning of scalp hair** (100%)
- ❑ Characteristic dermatologic pathology (96%)
- ❑ Short stature less than 160cm (95%)

Additional signs and symptoms:

- ❑ Thin limbs (present in 98%)
- ❑ Pinched facial features (96%)
- ❑ **Osteoporosis** (91%)
- ❑ Voice change (89%)
- ❑ Hypogonadism (80%)
- ❑ Type 2 diabetes mellitus (71%)
- ❑ Soft tissue calcification (67%)
- ❑ Neoplasm(s) (44%)
- ❑ **Atherosclerosis** (30%)

- **Definite WS:** 4 cardinal signs and 2 additional signs;
- **Probable WS**: the first three cardinal signs and two additional signs;
- **Possible WS**: Either cataracts or dermatologic alterations and four additional signs;

Identification of biallelic *WRN* pathogenic variants on molecular genetic testing confirms the diagnosis if clinical features are inconclusive.

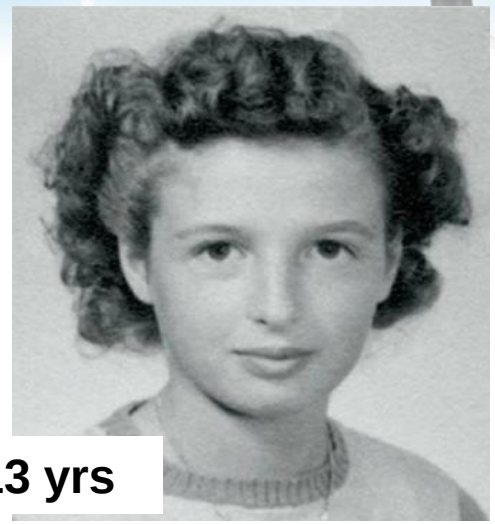
Skin findings in Werner s-me: Wrinkling, a sclerodermalike appearance with nose and lip atrophy, skin atrophy, deep, chronic ulcers around the ankles

https://www.ncbi.nlm.nih.gov/books/NBK1514/

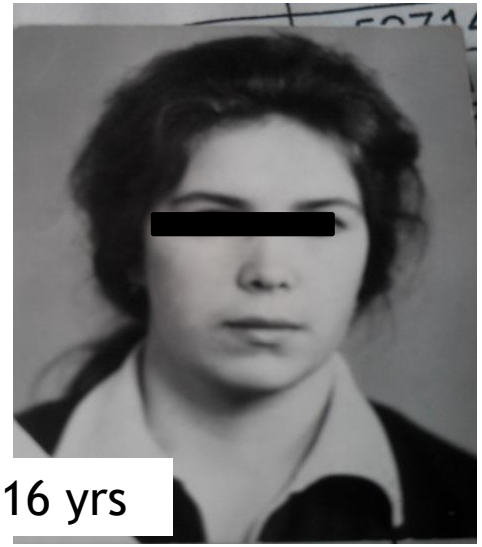
Werner syndrome?

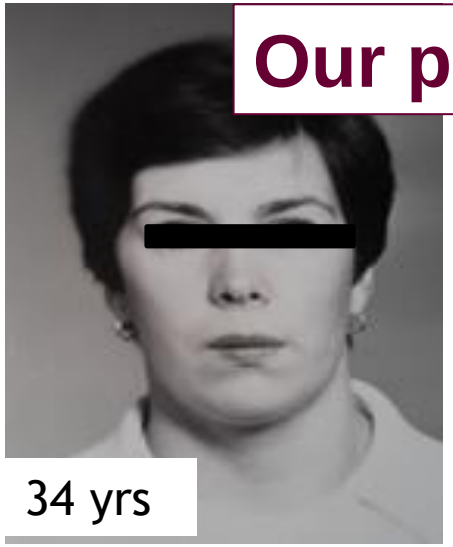

15 yrs


48 yrs

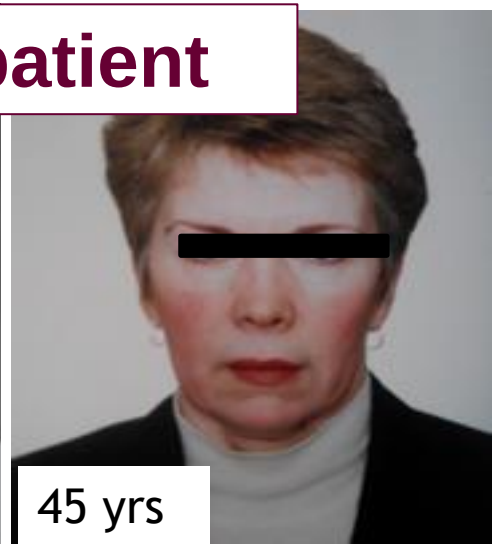

13 yrs

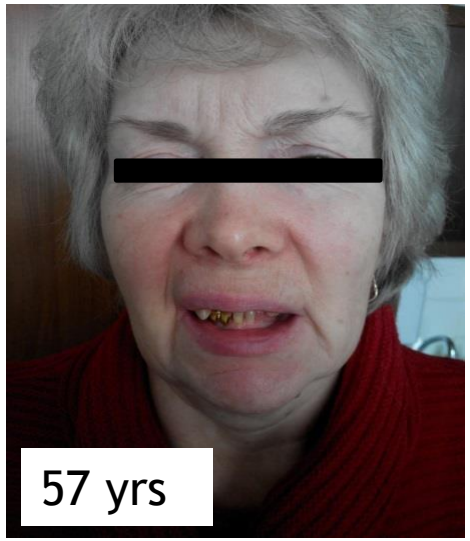

56 yrs


16 yrs


34 yrs

Our patient


45 yrs


57 yrs

http://www.senescence.info/WS.jpg

Conclusion

- Weber-Christian disease in our patient developed on the background of long course autoimmune thyroiditis with impaired function of the thyroid gland (hypothyroidism) and unstable hormonal status, after surgery (hysterectomy, ovarectomy) that exacerbated hormonal imbalance.
- Diagnosis of the disease Weber-Christian was made a few years after the onset of symptoms, which is due not only to the late referral of the patient for medical assistance, but also the weak medical vigilance in relation to rare diseases.
- This clinical case is an illustration of the fact that the key factors for the early diagnosis of rare diseases are a careful history taking, attentive and accurate approach to the patient, as well as a systematic analysis of laboratory and instrumental surveys.

Thank you for attention!

Questions?