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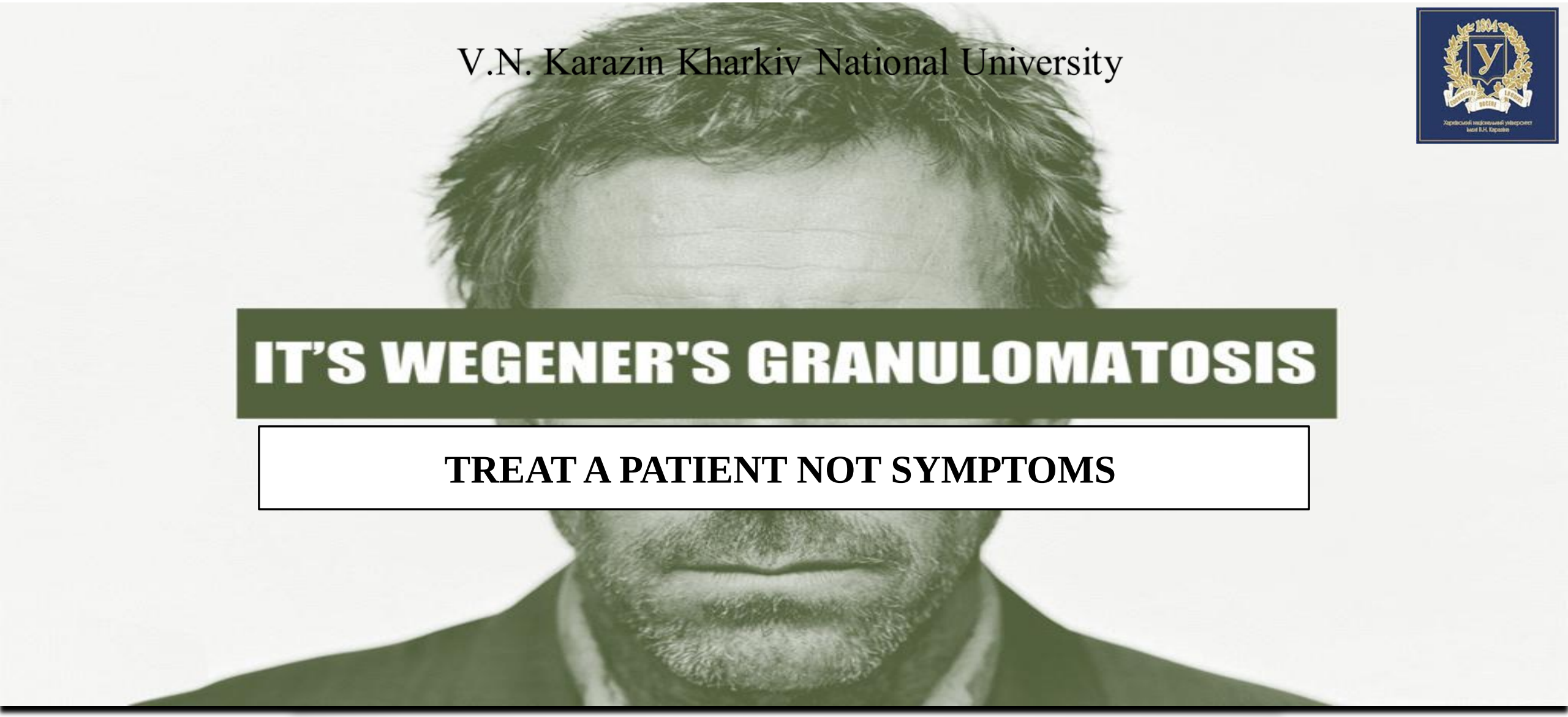

IT'S WEGENER'S GRANULOMATOSIS

TREAT A PATIENT NOT SYMPTOMS

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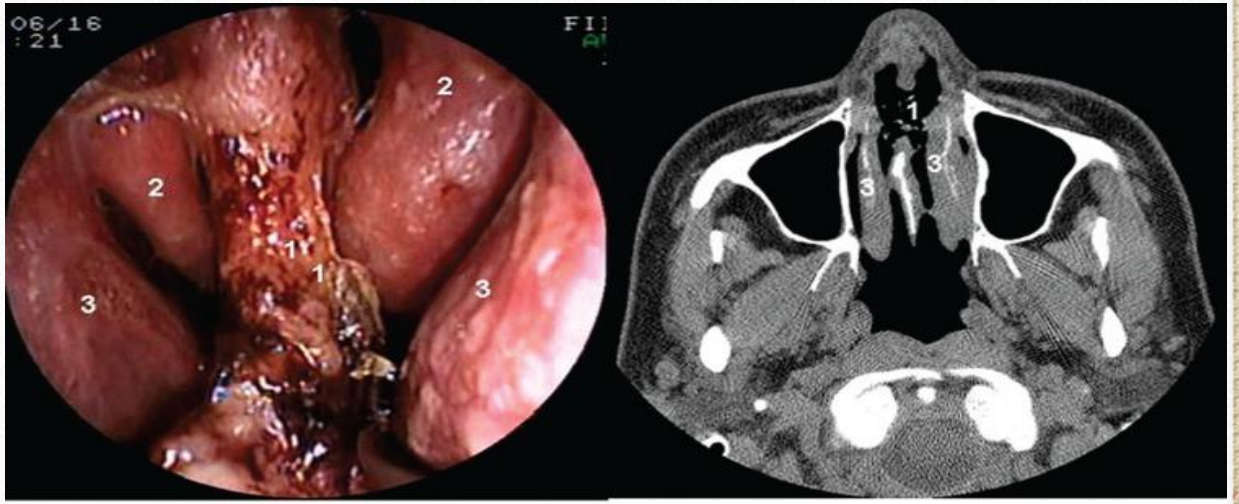
Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a rare multisystem autoimmune disease of unknown etiology. Its hallmark features include necrotizing granulomatous inflammation and pauci-immune vasculitis in small- and medium-sized blood vessels.

Otorhinolaryngologist is the first physician to contact for the majority of patients with GPA. This diagnosis must always be taken into consideration in patients with recurrent upper respiratory tract infections, otitis, mucosal ulcers and laryngitis. Proper and early diagnosis is crucial for imminent therapy implementation and allows avoiding irreversible organ damage.

Wegener's can be divided into two types:

- Limited GPA: (ENT± Lung) involvement
- Systemic GPA: [(ENT± Lung)+ Kidney] involvement



The aim of the clinical case presentation was to remind about an importance of each patient management systemically not symptomatically, with paying attention on effective differential diagnostics in case of resistant to treatment prescribed patients

OUR PATIENT

- Patient Ch.S.V.

- female
- 29 y. old
- former school teacher
- city resident

was admitted 04-feb-2017 in 25 Kharkiv city hospital by ambulance with diagnosis: Bronchial asthma attack.

of admission: 05 – September – 2015

COMPLAINTS

Patient was admitted 04-feb-2017 with complains on:

- body temperature 38°C
- ankles, hands, feet joints arthralgia
- breathlessness
- palpitation periodically
- dyspnea and periodical cough with viscous sputum
- partial hearing loss

ANAMNESIS MORBI (1)

- Patient was sick from august 2016, when during Ist trimester of pregnancy she presented with high temperature 38°C and nasal stuffiness for the first time. She was treated by otorhinolaryngologist with diagnosis of allergic rhinitis. Medical miscarriage in 8th week.

- Gradually she developed cough with periodical haemoptysis, pain in the throat, muco-purulent nasal discharge. Due to reoccurrence of body temperature 38°C and pitting oedemas with pain in ankles she was consulted in Poltava regional hospital by otolaryngologist, pulmonologist and rheumatologist with conclusion:
  i. chronic bronchitis,
  ii. chronic antritis,
  iii. reactive arthritis.

Patient was treated with: antibacterial, anti-inflammatory and anti-allergic drugs (exact drugs she couldn’t name). Despite slight improvement she still noticed presence of periodical body temperature elevation and nasal discharge. Also in this period of time she noticed changes in her nose shape.

ANAMNESIS MORBI (2)

- In autumn 2016 she was treated 7 days in Poltava hospital with diagnosis of Pneumonia
- From 22-nov-2016 till 29-nov-2016 patient was treated in Regional Kharkiv hospital with diagnosis:
  i. Community-acquired bilateral pneumonia, right sided partial spontaneous pneumothorax.
  ii. Bilateral catarrhal-edematous antritis.
  iii. Chronic bilateral perceptual-cum-neurological deafness.
  iv. Reactive oligoarthritis (unknown genesis), with ankle joints affection.
  v. Hypotrophy syndrome.
  vi. Chronic anemia. Thrombocytosis of unknown genesis.
  vii. Mitral valve prolapse I degree with regurgitation I degree. Chronic heart failure 1 stage.

ANAMNESIS MORBI (3)

- She was treated with:
  i. reosorbilact,
  ii. enoxaparin,
  iii. pantoprazole,
  iv. glucose 5%,
  v. dexamethasone,
  vi. K+ chlorine solution,
  vii. theophylline,
  viii. fluconazole,
  ix. meropenem,
  x. diclofenac

She felt better but without significant improvement.

Hospitalization in the rheumatology department was advised to enable definitive diagnosis and exclusion of systemic connective tissue disorder but patient refused.

Recommendation for additional laboratory investigations as ANCA, anti-cardiolipin IgG,M; LE-cells, ANA, etc was advised.

ANAMNESIS MORBI (4)

05-dec-2016 she noticed relapse of symptoms (cough with bloody-purulent sputum, dyspnea at rest, numbness of low extremities, purulent discharge from ear, t – 38°C, hair and weight loss) and by 12-dec-2016 she was urgently admitted in the rheumatology department of Kharkiv regional hospital and then due to heaviness of her state she was transferred to ICU department.

- Chest X-ray: polysegmental pneumonia
- Chest CT: infiltration in S1-S2, S3-S6, fibrosis after infiltration in S4
- Bronchoscopy: bilateral diffuse bronchitis III st., fibrinous inflammation, Streptococcus epid.
- 17.12.16: Sputum culture: S. aureus 10^2, sensitive to cefazolin, cefepime, ceftriaxone, amoxicillin, meropenem, amikacin, ofloxacin, clindamycin
- 28.12.16: Sputum culture : Candida, sensitive to clotrimazole, nystatin
- CBC: anemia, leukocytosis with left shift, thrombocytosis
- Urine: leukocyturia, proteinuria, hematuria, 24 hours proteinuria - 0,98 g/l
- 20.12.16: glycemic profile 6,0 – 12,3 – 13,5 – 10,0 mmol/l
- Ultrasound conclusion from 14.12.16 : Sclerotic changes of aortic and mitral valves. Mitral regurgitation II degree. Pulmonary hypertension II degree (32 mmHg). Hepatomegaly and adipose changes of liver. Chronic cholecystitis. Chronic pyelonephritis.

ANAMNESIS MORBI (5)

- She was discharged with diagnosis:
  i. Community-acquired right-sided poly-segmental pneumonia, 3rd clinical group. Chronic bronchitis, exacerbation. LF I-II stage.
  ii. Chronic Kidney Disease II stage: secondary nephropathy.
  iii. Candydomycosis. Peripheral lymphadenopathy.
  iv. Polyneuropathy of upper and low extremities, vegetal-sensual form.
  v. Reactive oligoarthritis (unknown genesis), with ankle joints affection. Hypotrophy syndrome.
  vi. Metabolic cardiomyopathy. Mitral valve prolapse I degree with regurgitation II degree, pulmonary hypertension I stage. CHF 0 stage.
  vii. Chronic anemia. Thrombocytosis of unknown genesis with haemorrhagic syndrome (upper and low respiratory tracts, kidneys involvement).
  viii. Chronic atrophic rhino-pharyngitis. Acute left-sided purulent middle otitis, tympanum second membrane formation after acute otitis. Chronic subatrophic erosive laryngo-tracheitis. Acute bilateral catarrhal-edematous antritis, reconvalescent.
  ix. Diabetes mellitus, firstly diagnosed.
  x. Hypocalcaemia.
  xi. Systemic vasculitis? Blood disorder?

ANAMNESIS MORBI (6)

- During last hospitalization in Kharkiv region hospital in December 2016, several councils of physicians with differential diagnostics between:
  i. ANCA - associated vasculitis,
  ii. Goodpasture syndrome
  iii. Sepsis

Despite results of laboratory investigations: cANCA 1,05 U/l (N-till 1U/l), ANA-negative, IgM to cardiolipin – negative, etc. these diagnoses weren't confirmed. She was recommended to continue treatment with:

i. methylprednisolone 12 mg daily,
ii. moxifloxacin 400 mg daily 10 days,
iii. biseptol (sulfamethoxazole+trimethoprim) 480 mg 2 times daily,
iv. nystatin 500 mg daily 14 days, Ca supplements,
v. consultation of hematologist and bone marrow trepan biopsy.

ANAMNESIS VITAE

- Hereditary diseases are not identified
- Allergic history - not burdened
- Childhood infections - no
- Sexually transmitted diseases were denied
- Smoker - no, does not abuse alcohol
- Hyperglycemia from November 2016 - 7,6mmol/l

OBJECTIVE STATUS

- Conciseness - clear, state –severe, body position – active, 37,8°C, SpO_2 -94%.
- Patient can orientate to place, time, and personality
- Saddle shape nose deformity.
- Pale skin and mucosae. Thyroid: not enlarged, soft. Peripheral lymphatic nodes – not enlarged.
- Smoothed contours of ankle joints, with moderate functional limitations in the ankles joins. Cyanosis of the skin in the area of proximal interphalangeal hands 2,3,4 joints.
- BR – 26-30 /min. Chest is symmetrical, active respiratory muscles participation in breathing, retraction of intercostal spaces. Lung percussion: dull sound in lower parts. Lung auscultation: weak breathing and whizzing and rales in lower lung lobes.
- Borders of the heart: without clinically significant changes. Heart auscultation: rhythmic, heart tones – muffled, systolic soft murmur over all points of auscultation. HR - 140 bts/min
- Pulse – rhythmic, weak, 140 beats/min. BP- 120/70 mm Hg.
- Abdomen: normal size, symmetric, unpainful.
- Liver: +2cm, moderate density, no pain during palpation in right hypochondrium
- Spleen: not palpated
- Pasternatsky symptom – negative from both sides
- Edemas: absent

COMPLETE BLOOD COUNT

	22.11.16	26.11.16	12.12.16	27.12.16	03.01.17	06.02.17	13.02.17	Normal Range
Hemoglobin, g/l	**87**	**77**	**94**	**85**	**65**	**70**	**75**	130 – 160
Red blood cells, 1012	**4,02**	**3,33**	**3,6**	**3,2**	**2,5**	**2,5**	**2,8**	4.0 – 5.0
Color index	**0,66**	**0,7**	**0,77**	**0,79**	**0,79**	**0,84**	**0,84**	0,85 – 1,05
White blood cells, 109	**10,5**	**8,7**	**12,1**	**20,3**	**11,1**	**9,9**	**6,7**	4 - 9
ESR, mm/h	**42**	**42**	**50**	**40**	**11**	**31**	**45**	1 -10
Bands	**8**	**6**	**6**	**1**	**2**	**6**	**1**	1.06 – 6%
Segments	**82**	**74**	**79**	**73**	**70**	**72**	**58**	47 – 72%
Eosinophils	**0**	**5**	myelocytes		**1**	**1**	**2**	0.5 – 5%
Monocytes	**2**	**5**	**4**	**11**	**6**	**3**	**7**	0.1 – 3%
Lymphocytes	**8**	**10**	**10**	**15**	**21**	**18**	**32**	19 – 37 %
Platelets	**781**	**472**	**1005**	**259**	**265**	**180**		180-320

Conclusion: thrombocytosis, moderate anemia, leukocytosis

URINE TEST

	22.11.16	23.12.16	03.01.17	04.02.17	07.02.17	N
ρ	1.008	1,010	1,007	1,003	1,007	1.001 – 1.040
glucose	-	-	-	-	-	-
protein	0.2	1,8	1,9	0,054	0,216	- , g/l
WBC	4-5	25-30	½ of field	10-15	½ of field	1-2
hyaline casts	-	1-2	3-4	4-5	2-3	-
granular casts	-	-	-	5-6	1-2	-
pH	6,0	6,0	6,0	6,0	6,0	5-7
RBC	8-10	all field	20-30	35-40	6-8	0
other	keton bodies	menses	fungi	-	salts	

24 hours proteinuria - 0,98 g/l

Conclusion: proteinuria, leukocyturia, hematuria

BIOCHEMISTRY TEST DATA (1)

	22.11.16	20.12.16	03.01.17	04.02.16	07.02.17	N
Glucose, mmol/l	**6,1**	**4,9**	**4,2**	**5,2**	**7,4**	3.38 – 5.55
Total protein, g/l		**53**	**47,6**	**66**	**67**	
Total bilirubin, mkmol/l	**11,0**	**12**	**9**	**9,8**	**9,6**	8,6 – 25,5
AST, U/l	**37,8**	**51,2**	**20,2**	**20,2**	**21,2**	10 - 45
ALT, U/l	**47,2**	**25,5**	**14,5**	**14,5**	**15,6**	10 - 68
Protrombin index, %	**82,1**	-	-	-	**83**	85-105
Fibrinogen, g/l	**7,8**	-	-	-	-	
Creatinine, mkmol/l	**80,8**	**124**	**138**	**88**	**87**	80 – 115
K, mmol/l	**4,36**	**4,61**	**5,62**	-	-	3,5-5,1
Fe, mmol/l		**21,9**	**11,9**	-	-	9,0 – 23,3
Cl, mmol/l	**102**	-	-	-	-	
Na, mmol/l	**141,5**	-	-	-	-	135-145

Conclusion: elevation of creatinine levels, periodical hyperglycemia

BIOCHEMISTRY TEST DATA (2)

12.12.16. malaria CBC scopy – negative
12.12; 21.12; 22.12; 23/12/16 – blood culture – no grows, negative.
09.02.17: sputum culture: MBT –negat, S. pneumonie 10^8 , sensitive to ceftriaxone.

20.12.16. seromucoids - 721 U (N- 135—200); uric acid - 329 mkmol/l (N 150 — 350 mkmol/l).
27.12.16. seromucoids - 469 U (N- 135—200); uric acid -350 mkmol/l.

20.12.16. CRP - 60 mg/l (N 0-5); rheumatoid factor -120 mU/l (N-negat).
26.12.16. CRP – 36 mg/l (N 0-5);
20.12.16: AB to Tbs – negative.
30.12.16: AB to glomerular basal membrane IgG - negat.,
20.12.16: HBC and HBV summarized antigens – negat.
20.12.16: cANCA -1,05 U/l (N till 1,0), anticardiolipin IgM - 1,11 U/l (N till 7 U/l), ANA – negat., LE-cells – negat., ACCP – negat., IgG to herpes – negat., IgG to CMV – negat., IgM to phospholipin and glycoprotein – negat, HIV – negat., VCA IgM and VCA IgG – negat., PCR for herpes, CMV, VCA – negat., RW – 13.02.17 №9284-negat.

CHEST X-RAY

04.02.17

On Chest X-ray in a direct and the right lateral projection on an inspiration and an exhalation is defined emphysema, diffuse pneumosclerosis. On the right, in the lower lobe, there is a focus of the lung tissue low transparency due to infiltration without clear contours. In the basal zones on both sides, there is an increase in pulmonary pattern according to the strend type. Sinuses are free. Ordinary diaphragm, normal excursion. Cardiovascular shadow within normal limits.

Conclusion: Pneumosclerosis. Right-sided pneumonia.

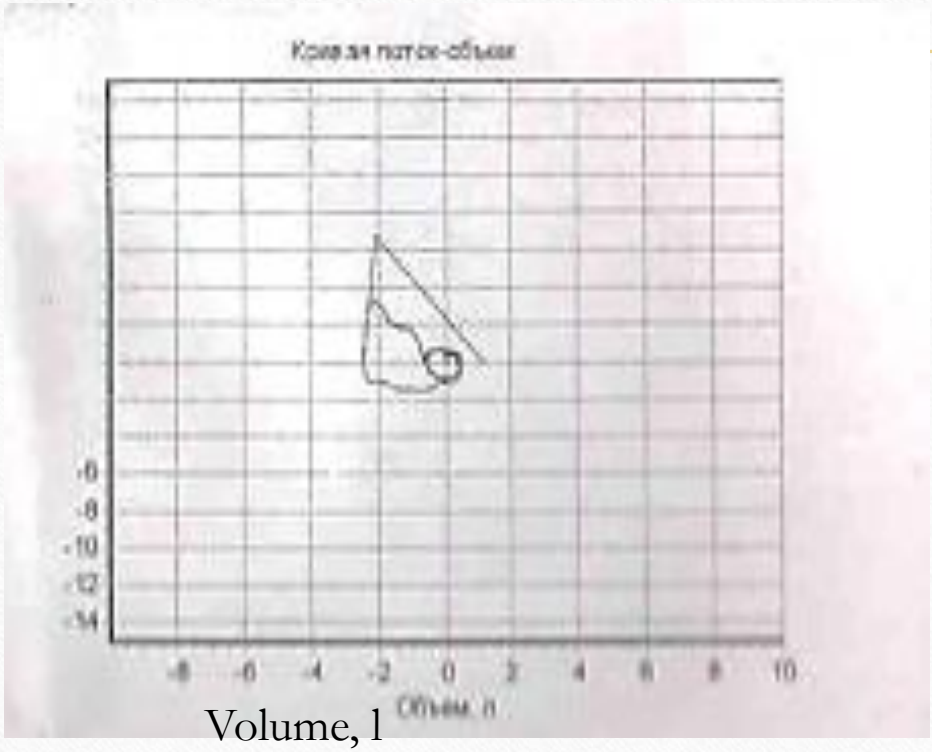
15.02.17

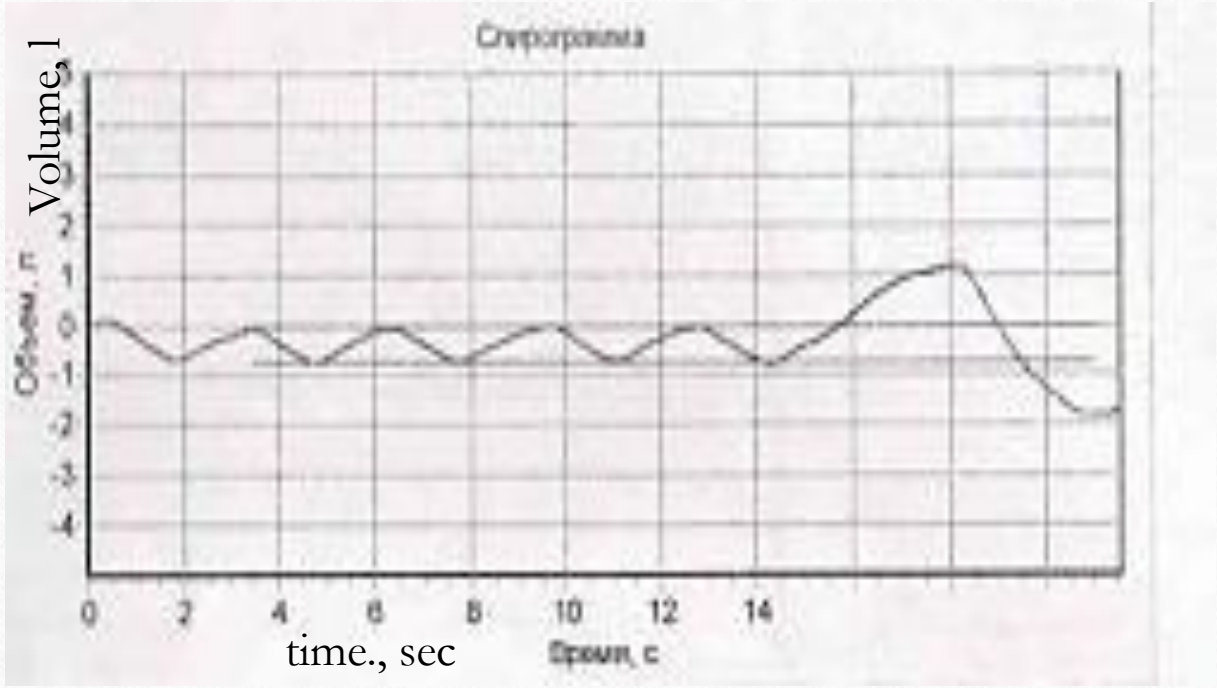
On the control Chest X-ray positive dynamics seen. Infiltration is not present. There is some increase of the pulmonary pattern in the medial parts, because of the vascular component. Structural roots. Diaphragm is normal. Sinuses are free. Enlargement of heart shadow as the left border of the heart is widened.

Conclusion: the residual changes after pneumonia.

OTHER INVESTIGATIONS

Spirometry from 14.02.17. – VLC – 2,99l (84,3% from normal), FEV_1, l – 1,67 (54% from normal), FEV_1/FVC – 99,7 (0,9). Conclusion: stenosis of intrathoracic respiratory ways.





ECG from 04.02.17: sinus rhythm, sinus tachycardia with HR -150 beats in min., metabolic disturbances

SPECIALIST'S CONSULTATIONS

Otolaryngologist – Chronic rhino-pharyngitis. Chronic left-sided cochlea-neuritis.

Neuropathologist - polyneuropathy of upper and low extremities, vegetal-sensual form.

Pulmonologist– taking into consideration clinical and laboratory data can be made conclusion about primary ANCA – associated systemic vasculitis (it is necessary to make differential diagnosis between Goodpasture syndrome and Wegener's granulomatosis).

MEDICATIONS PRESCRIBED IN HOSPITAL before establishing diagnosis

Preliminary diagnosis in ED during hospitalization was:

i. Community-acquired pneumonia III clinical group, LF II stage
ii. Anemia of unknown genesis.

- levofloxacin 500mg 1 time\day from admission
- ceftriaxone 2g IM 1 time/day from admission
- inhalations with moistened O2 from admission
- dexamethasone 8mg IV 1 time daily from admission
- Hartmann’s solution IV 200,0 ml from admission
- ivabradin 5 mg 2 time\day from admission
- acetil-cystein 400mg a day from admission
- ipratropium bromide+fenoterol inhalation 2 times/day

ACR-EULAR diagnostic criteria proposed for granulomatosis with polyangiitis (2017)

Clinical Items & Their Scores

•Bloody nasal discharge, ulcers, crusting or sino-nasal congestion: **3**
•Nasal polyps: –4
•Hearing loss or reduction: **1**
•Cartilagenous involvement: **2**
•Red or painful eyes: 1

Test Result Items & Their Scores

•c-ANCA- or PR3-antibody positive: **5**
•Eosinophil count ≥1 (x109/L): –3
•Nodules, mass or cavitation on chest imaging: **2**
•Granuloma on biopsy: 3

the patient must reach a score of 5 or more to be classified as having GPA.

Our patient score is 13

https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines

COMPLETE DIAGNOSIS

- Generalized granulomatosis with polyangiitis with involvement of upper and lower respiratory ways, kidneys.
- Chronic rhino-pharyngitis. Chronic left-sided cochlea-neuritis.
- Polyneuropathy of upper and low extremities, vegetal-sensual form.
- Metabolic cardiomyopathy. Mitral valve prolapse I degree with regurgitation II degree. Pulmonary hypertension I stage. CHF 0 stage.
- Anaemia of chronic disease, moderate.

MEDICATIONS PRESCRIBED IN HOSPITAL after establishing diagnosis

- methylprednisolone in dosage 64 mg/day
- methotrexate in dosage 20mg/day in combination

RECOMMENDATIONS:

- The mainstay of treatment for granulomatosis with polyangiitis (GPA) is a combination of corticosteroids and cytotoxic agents. The choice of methotrexate with glucocorticoids combination as initial therapy was based on absence in our patient case non-organ-threatening and non-life-threatening disease (no evidence for "active" glomerulonephritis or no organ-threatening or life-threatening manifestations, patients may have rhinosinusitis, arthritis, and/or pulmonary nodules). For our patient was prescribed a combination of methylprednisolone in dosage 64 mg/day and methotrexate in dosage 20mg/day for 1 month with adjustment of therapy in future.
- The association in nondiabetics between HbA1c and hyperglycemia during critical illness results from stressing normally adequate homeostatic mechanisms: patients with the greatest baseline reserve, as reflected by HbA1c, have less hyperglycemia. From November 2016 our patient has hyperglycemia, so it was recommended glycemic levels control (fasting glucose, HbAc1) as one of signs of improvement and possible therapy prescribed complications.
- Patients with GPA should have regularly scheduled follow-up visits with the physician primarily responsible for managing his or her disease. Since recurrences occur frequently, patients should be monitored closely clinically, with radiologic studies and laboratory examinations that include renal function, erythrocyte sedimentation rate (ESR), ANCA levels, and urinalysis.
- Prophylaxis against *Pneumocystis* pneumonia is essential while patients are receiving conventional therapy for GPA. This can be achieved with trimethopim-sulfamethoxazole single-strength once daily or double-strength formulation three times per week. Dapsone 100mg daily can be used in sulfa-allergic patients. Also baseline bone mineral density should be evaluated because of high risk for glucocorticoid-induced osteoporosis.

CONCLUSION

Routine laboratory tests are nonspecific in granulomatosis with polyangiitis. Rheumatoid factor is positive in a low titer in two thirds of patients, whereas antinuclear antibody is present in 10-20% of patients. Whether tissue diagnosis is always required for GPA remains controversial. As the therapy for severe GPA is not benign, tissue diagnosis is recommended if a biopsy site is available, provided that the patient understands the risks of the procedure. C-ANCA directed against PR3 is most specific for GPA.

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Thank
you