Clinical Case IgG4 Associated Disease (Mikulich's Disease)

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Abstract

The article presents a description of a rare IgG4 associated disease - Mikulich's disease. The disease is characterized by a slowly progressive symmetrical painless increase in the lacrimal and salivary glands, an increased concentration of immunoglobulins of the IgG4 subclass, infiltration of tissues of various organs by IgG4-plasma cells. The etiology of the disease is considered unidentified. For the treatment of BM, GC is mainly used. Promising is anti-B-cell therapy.

Keyword: IgG4 Associated Disease; Mikulich's Disease; Clinic; Diagnostics; Treatment

Abbreviations

CBC: Complete Blood Count; Er: Erythrocytes; Hb: Hemoglobin; CP: Color index; Tr: Platelets; Ht: Hematocrit; Leu: Leukocytes; Eo: Eosinophils; P: Bacilli; S: Segments; L: Lymphocytes; M: Monocytes; ESR: Sedimentation Rate of Erythrocytes; CT: Computed Tomography; MRI: Magnetic Resonance Tomography; APPT: Activated Partial Thromboplastin Time; INR: International Normalized Ratio

Introduction and Case Report

On August 2, 2019, the 37-year-old patient was admitted to the Department of Otolaryngology of city clinical hospital № 12 of Kazan, Russia. He complained of a pressing headache in the left fronto-parietal region, drooping of the upper eyelid of the left eye, nasal congestion and general weakness.

Anamnesis morbi: The patient has been sick for 3 years. The course of the disease worsened in July 2019. On July 8, 2019, he was admitted to the otolaryngology department of city clinical hospital № 12 of Kazan, Russia. He was given a preliminary diagnosis: Exacerbation of bilateral chronic polypus-purulent rhinosinusitis. Neoplasm of the right maxillary sinus and ethmoid labyrinth on the right.

The patient underwent the following laboratory and instrumental studies (normal values are indicated in brackets):

- Complete blood count (CBC) from 07/08/2019: erythrocytes (Er): 5.4 x 10^{12}/l (3.7 - 4.7 x 10^{12}/l), hemoglobin (Hb): 151 g/l (120 - 140 g/l), color index (CP): 0.9 (0.85 - 1.05), platelets (Tr): 471 x 10^{9}/l (200 - 400 x 10^{9}/l); Hematocrit (Ht): 47.7%; (35 - 50%) Leukocytes (Leu.): 11.7 x 10^{9} (4.0 - 9.0 x 10^{9}/l), eosinophils (Eo.): 1% (0 - 5%), bacilli (P.): 3% (1 - 6%), segments (S.): 76% (47 - 72%), lymphocytes (L.): 12% (18 - 38%), monocytes (M.): 8% (3 - 11%), Sedimentation rate of erythrocytes (ESR): 4 mm/hour (2 - 15 mm/hour). Glucose: 7.6 mmol/L (3.5 - 5.5 mmol/L).

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- Urinalysis dated 07/08/2019: Urine specific gravity 1020, transparent, color - straw-yellow, acid reaction, protein - negative, Leukocytes 0-1 in the field of view, Erythrocytes 0 in the field of view, epithelium 0-1 in the field of view.
- Blood glucose from 07/09/2019: 5.6 mmol/l (3.5 - 5.5 mmol/l).
- Rapid plasma reagin from 07/08/19: Negative.

07/09/2019 the patient underwent a puncture of the right maxillary sinus.

The patient underwent spiral computed tomography (CT) of the paranasal sinuses on July 10, 2019. The result: The curvature of the nasal septum to the right side is determined, the parietal thickening of the mucous membrane in the maxillary sinuses is visualized, the right one is totally blocked, the left subtotally, parietal thickening of the mucosa, in the main sinus labyrinth, in the right half of the frontal sinus.

Most of the cells of the right mastoid process are blocked, in some cells there are meniscus-like levels, the cavity of the middle ear is unremarkable, parietal thickening of the mucosa in the mastoid cave. Conclusion: According to the CT picture, there are signs of pansinusitis, right-sided mastoiditis, antritis, curvature of the nasal septum (Figure 1 and 2).

![Figure 1: Computed tomography of the brain from 10.07.2019, before the operation to the patient.](image1)

![Figure 2: Computed tomography of the brain from 10.07.2019, before the operation to the patient.](image2)
On July 12, 2019, the patient underwent endoscopic correction of the nasal septum and endoscopic hemisinusotomy on the right.

On July 12, 2019, a cytological study was performed. Result: Proliferation of ciliated epithelium with squamous cell metaplasia, proliferation of fibrocytes and fibroblasts, multinucleated cells of the foreign body type. A viral lesion is not excluded.

On July 17, 2019, a histopathological examination was carried out. Result: Fibrous tissue, areas of central necrosis, mucous membrane with inflammatory infiltration, epithelioids are determined in some sections. Eliminate tuberculosis.

On July 22, 19, the patient underwent a CT scan of the chest. Result: Pathological changes in the skeletal system were not identified. No focal infiltrative changes were found in the lungs. Calcinate was found in the root of the right lung. The pathology of the chambers of the heart was not identified. The fluid in the pleural cavities is not determined. Conclusion: Lungs without pathology.

The patient received a course of anti-inflammatory therapy: Solution Ceftriaxone 2.0 + Natrii chloride 0.9%-200 ml intravenous drip-feed, 1 time a day. Solution Keturolac 3% - 1.0 ml intramuscularly, 2 times a day. Solution Demerol 1% - 1.0 intramuscularly, 1 time a day. Tablet Loratadine 10 mg, 1 time a day. Solution Calcium gluconate 10% - 10.0 ml intravenous push, within 5 days.

The patient was given the final diagnosis: Exacerbation of bilateral chronic polypous-purulent rhinosinusitis. Neoplasm of the right maxillary sinus and ethmoid labyrinth on the right.

The patient's condition has improved and he was discharged home with outpatient follow-up on July 24, 2019.

In the postoperative period, the patient developed moderate ptosis of the upper eyelid of the left eye. He again began to worry about headaches in the left frontal region. His visual acuity in his left eye decreased. From 07/29/2019 to 08/02/2019, he was inpatient treatment at the neurology department of the city hospital No. 7 of Kazan with a diagnosis of Secondary rhinogenic bacterial meningitis, mild course. Right-sided acute exudative otitis media. Mastoiditis on the right. Chronic polynsinusitis. Amblyopia of the left eye. Retinal angiopathy.

The patient underwent CT scan of the paranasal sinuses on 07/29/19. Result: On a series of tomograms, the state after surgery on the right maxillary sinus is determined, there is a defect in the medial wall, parietal thickenings in the maxillary sinuses are visualized, the left one is closed subtotally, in the cells of the ethmoid labyrinth, in the front sinuses (divided by septa), in the main sinus. Revealed signs of bilateral mastoiditis.

The patient underwent a brain MRI on July 30, 2019: Conclusion: signs of meningitis in the region of the left cerebral hemisphere. Parietal edema of the mucous membrane in the frontal sinus, sphenoid sinuses. Right-sided otitis media, mastoiditis. Hyperplasia of the mucosa in both maxillary sinuses with parietal lumen of the right side, total left (polyps). The enlarged lacrimal gland on the left, while maintaining the usual intensity of the MR signal in all modes, with the provision of a compressive effect on the left eyeball and the muscle that lifts the upper eyelid on the left, which is slightly thickened.

On 02.08.2019 the patient was transferred to the otolaryngology department of the city clinical hospital № 12 for further treatment, where he received treatment from 02.08.2019 to 02.09.2019.

Anamnesis vitae: The patient is married. Has 2 healthy children. He does not have infectious hepatitis, sexually transmitted diseases, tuberculosis, or allergic reactions. There were no blood transfusions. Has no bad habits. Heredity is not burdened. In the past he had chronic rhinosinusitis, chest trauma in 2018. Has bad habits: smokes for about 20 years, alcohol does not abuse.
Status praesens objectives: The patient’s height is height 180 cm, weight is 90 kg, body mass index is 27.78. The general condition of the patient is satisfactory, the consciousness is clear. The patient’s skin and visible mucous membranes are a physiological color. The patient’s peripheral lymph nodes are not enlarged. No edema. The patient’s musculoskeletal system is normal. The patient’s respiratory system are normal, the number of respiratory movements - 17 per minute.

The patient’s breathing is vesicular; wheezing is not heard. Patient’s cardiovascular system: heart rate 70 per minute, satisfactory filling, blood pressure 120/80 mm Hg. The boundaries of the heart are within normal limits. Heart sounds are muffled. The patient’s digestive system: the tongue is clean. The abdomen is soft and symmetrical. On palpation, the soreness of the pancreas in the duodenal region is determined. The patient’s liver and spleen are not enlarged. The patient’s urinary system was unremarkable. Pasternatsky’s symptom is negative on both sides (No CVA tenderness on percussion. Urination is painless). Diuresis is normal.

The following laboratory and instrumental studies were carried out:

- **CBC dated 02.08.2019:** Er.: 4.6 x 10^{12}/l, Hb: 126 g/l (120 - 140 g/l); CP: 0.88 (0.85 - 1.05), Tr.: 420 x 10^9/l (200 - 400 x 10^9/l), Ht: 41.0% (35 - 50%), Leu.: 11.6 x 10^9/l (4.0 - 9.0 x 10^9/l); E.: 1% (0 - 5%), P.: 1% (1 - 6%), S.: 77% (47 - 72%), L.: 13% (18 - 38%), M.: 8% (3 - 11%), ESR: 24 mm/hour (2 - 15 mm/hour).

- **Glucose from 08/02/2019:** 7.6 mmol/L (3.5 - 5.5 mmol/L).

- **CBC dated 06.08.2019:** Er.: 4.8 x 10^{12}/l (3.8 - 5.1 x 10^{12}/l), Hb: 132 g/l (120 - 140 g/l), CP: 0.82 (0.85 - 1.05), Tr.: 473 x 10^9/l (200 - 400 x 10^9/l), Ht: 44.1% (35 - 50%), Leu.: 13.2 x 10^9/l (4.0 - 9.0 x 10^9/l); P.: 3% (1-6%), S.: 60% (47-72%), L.: 30% (18 - 38%), M.: 7% (3 - 11%); ESR: 51 mm/hour (2 - 15 mm/hour).

- **CBC dated 08/13/2019:** Er.: 4.6 x 10^{12}/l (3.8 - 5.1 x 10^{12}/l), Hb: 124 g/l (120 - 140 g/l), CP: 0.80 (0.85 - 1.05), Tr.: 448 x 10^9/l (200 - 400 x 10^9); Ht: 41.0% (35 - 50%), Leu.: 12.5 x 10^9 (4.0 - 9.0 x 10^9/l); E.: 2% (0 - 5%), P.: 1%, C.: 73%, L.: 18%, M.: 6%, ESR: 60 mm/hour (2 - 15 mm/hour).

- **CBC from 08/26/2019:** Er.: 4.0 x 10^{12}/l (3.8 - 5.1 x 10^{12}/l); Hb: 108 g/l (120 - 140 g/l), L.: 10.1 x 10^9/l (4.0 - 9.0 x 10^9/l); Ht: 34.9% (35 - 50%), Tr.: 407 x 10^9 (200 - 400 x 10^9); S.: 67.6% (47 - 72%), L.: 19.8% (18 - 38%), M.: 11.8% (3 - 11%).

- **Uranalysis dated from 08/02/2019:** Urine specific gravity: 1.015, protein: negative, Leu: 0-2, Er: 0 in the field of view, epithelium 0-2 in the field of view.

- **Uranalysis dated from 23.08.2919:** Urine specific gravity: 1.002, protein: negative, Leu.: 0-2 in the field of view.

- **Biochemical blood test from 08/02/2019:** Total bilirubin 6.6 μmol/L (5 - 21 μmol/L), direct bilirubin 2.6 μmol/L (up to 3.4 μmol/L), indirect bilirubin 4.0 μmol/L (1.7 - 17.0 μmol/L), blood urea: 4.1 mmol/L (2.8 - 7.2 mmol/L), blood amylase 47 U/L (22 - 80 U/l); total protein 73 g/l (66 - 83 g/l), ALT 38 u/l (<40 u/l); AST 18 U/L (<40 U/L), blood creatinine 58 μmol/L (59 - 104 μmol/L).

- **Coagulation profile from 08/02/2019:** Prothrombin 72% (80 - 100%), fibrinogen 2.7 g/l (2 - 4 g/l), activated partial thromboplastin time (APPT): 30.1; international normalized ratio (INR): 1.3 (up to 1.1).

- **Blood glucose from 08/06/2019 at 8:00:** 5.8 mmol/L, 11:00: 4.5 mmol/L, 13:00: 4.8 mmol/L. Blood glucose from 08/07/2019 at 8:00 - 5.6 mmol/L. Blood glucose: 08/08/2019 8:00 - 6.7 mmol/L.

- **Biochemical blood test from 08/13/2019:** Calcium: 1.24 mmol/l (1.05 - 1.3 mmol/l), potassium: 4.55 mmol/l (3.5 - 5.5 mmol/l), sodium: 140 mmol/L (N 135 - 155 mmol/l), total bilirubin: 9.9 μmol/L (5 - 21 μmol/L), direct bilirubin: 2.4 μmol/L (3.4 μmol/L), indirect bilirubin 7.5 μmol/l (1.7 - 17.0 μmol/l), blood urea 3.3 mmol/L (2.8 - 7.2 mmol/L), blood glucose: 5.7 mmol/L (N 4.1 - 5.9 mmol/L), blood amylase 47.3 U/L (22 - 80 U/L), total protein: 69.3 g/L (66 - 83 g/l), albumin: 34.0 g/l (35 - 52 g/l).

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- Total cholesterol: 4.2 mmol/L (up to 5.2 mmol/L), beta-lipoproteins: 2.6 mmol/L (up to 3.3 mmol/L), ALT: 20 U/L (⩽40 U/L); AST: 14 U/L (⩽40 U/L), serum iron: 5.0 μmol/L (10.7 - 32.2 μmol/L), alkaline phosphatase: 79.3 U/L (30 - 120 U/L), uric acid: 182 μmol/L (154 - 357 μmol/L), blood creatinine: 50 μmol/L (59 - 104 μmol/L), C-reactive protein (CRP) 80.2 mg/L (5 mg/L), rheumatoid factor: 6.1 IU/ml (up to 14 IU/ml), anti-streptolysin 0: 150 IU/ml (up to 200 IU/ml).

- Coagulation profile dated 08/13/2019: Quick’s value 75.3% (70 - 130%), fibrinogen: 4.8 g/l (2 - 4 g/l), APTT: 38.3, INR: 1.15 (up to 1.1).

- Vfjr b ckbcnjg.

- Rapid plasma reagin from 02.08.2019 is negative.

08/06/2019 a swab from the mucous membrane of the paranasal sinuses was taken from the patient (operational) Result: Enter was inoculated. faecalis. Resistant to ampicillin, cefotaxime, ceftazidime, cefepime, amikacin, imipenem. Sensitive to gentamicin, vancomycin.

Blood test for procalcitonin from 08/13/2019: procalcitonin - negative (less than 0.05 μg/l).

09/05/19 at the Republican Clinical Oncological Dispensary of the Ministry of Health of the Republic of Tatarstan, a microscopic description and conclusion of the histological undercut of blocks were made. Result: Pronounced chronic inflammation in the exacerbation stage, micronecrosis, microabsorption, multinucleated cells of resorption (Figure 3-6).

![Figure 3: Diffuse lymphoplasmacytic infiltration with granulocytes.](image)

![Figure 4: Lymphoplasmacytic infiltration with a multinucleated cell.](image)
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The result of the analysis of cerebrospinal fluid from 05/08/2019: color - colorless; transparency - transparent; protein - 0.132 g/l; glucose - 3.94 mmol/L; number of shaped elements in 1 mm$^3$ - 27.6; cellular elements (after centrifugation): Er. - 1-3 in the field of view (up to 4 cells), Lei. - 5-8-1 in the field of view (negative).

The result of the analysis of cerebrospinal fluid from 08/12/2019: color - colorless; transparency - transparent; protein - 1.3 g/l; the number of shaped elements in 1 mm$^3$ - 48; cellular elements (after centrifugation): Er. - 0-1 in the field of view; Leu. - 5-7-9 in the field of view.

The result of the analysis of cerebrospinal fluid from 13.08.2019: color - colorless, transparency - transparent, protein - 0.5 g/l, number of formed elements in 1 mm$^3$: 27.6, cellular elements (after centrifugation): Er. - 1-2 in sight, Leu. 7-9-13 in the field of view.

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The result of a cytological study of the cerebrospinal fluid from 08/12/2019: in the fluid sediment: Er. (should not be contained), Leu.: 2-3-5 in the field of view (should not be contained) - lymphocytes predominate (about 95-97%). In a cytological study of cerebrospinal fluid from 08/20/2019: shaped elements: 29.4 cells in mm³, protein: 1 g/l, before centrifugation: Er.: 0-0-1, Leu.: 0-0-2, after - Er.: 0-0-2, Leu: 1-2-3 in the field of view, glucose: 3.6 mmol/l.

The results of bacteriological inoculation of blood, urine, cerebrospinal fluid on the microflora from 08/13/2019: no microflora was found.

The result of the study of cerebrospinal fluid for meningococcus from 08/13/2019: Negative.

The result of a blood test for Human Immunodeficiency Virus, syphilis, antibodies to viral hepatitis B and C dated 08/13/2019: Negative.

Microscopic examination of sputum for Bacterium Koch three times from 08/13/2019: negative, Leu.: 20 - 80 in the field of view (small amount), flora: cocci (should not be present), diplococci (should not be present).

The result of the cytological study of cerebrospinal fluid from 08/20/19: formed elements: 29.4 cells in mm³, protein: 1 g/l, before centrifugation: Er.: 0-0-1, Leu.: 0-0-2, after: Er.: 0-0-2, Lake: 1-2-3 in the field of view, glucose: 3.6 mmol/l.

The result of the analysis of CSF for DNA for cytomegalovirus, herpesvirus types 1 and 2, herpesvirus type 6, Epstein-Barr virus from 08/20/2019: negative.

Electrocardiogram from 08/07/19: sinus arrhythmia with a heart rate of 87-93-101. The electric axis is normal. Tachycardia. Shortening the PQ interval (Figure 7).

![Electrocardiogram of the patient from 08/07/19.](image)
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The result of CT scan of the patient’s brain from 08/05/2019 compared with the CT data from 07/29/2019 - without significant dynamics.

The result of a CT scan of the brain from 08/12/2019: the curvature of the nasal septum to the right side, parietal thickening of the mucous membrane in the paranasal sinuses, postoperative bone defects in the medial maxillary sinuses, in the right half of the ethmoid labyrinth are determined.

Conclusion: According to the CT picture, the state after bilateral sinusitis, right-sided ethmoidotomy, signs of pansinusitis, pathological changes in the brain and skull bones were not found (Figure 8-11).

Figure 8: Computed tomography of the patient’s brain from 08/12/2019.

Figure 9: Computed tomography of the patient’s brain from 08/12/2019.
The result of a chest x-ray of the patient from 16.08.2019 and from 26.08.2019: lungs without pathology.

Result of MRI of the patient’s head with contrast from 08/22/2019: MRI - signs of previous meningitis.

The patient was consulted by a neurologist (06.08.2019). The diagnosis was made: compression neuropathy of the optic branch of the trigeminal nerve on the left, the optic nerve on the left, compression of the muscle that lifts the upper eyelid on the left. Prednisolone 90 mg intravenously was prescribed.
The patient was consulted by an endocrinologist (08/06/19) - diagnosis: transient hyperglycemia against the background of somatic trouble. The patient was recommended to control blood glucose at 21.00 - 6.00. If the condition worsens - observation by an endocrinologist at the place of residence.

The patient was consulted by an infectious disease specialist (15.08.2019). Was diagnosed with serous meningitis, possibly secondary, against the background of the underlying disease (ENT pathology). No data were found for infectious pathology. Recommended: to continue antibiotic therapy, to examine the cerebrospinal fluid for herpes viruses.

The patient was consulted by a tuberculotherapist (15.08.2019). No convincing evidence was found for tuberculous meningitis.

The patient was consulted by a pulmonologist (16.08.2019). Was diagnosed with chronic bronchitis in the acute stage. Recommended: Tablet Ambroxol 30 mg 3 times a day, Solution Prednisolone 90 mg intravenously drip in 200.0 ml of saline, continuation of antibacterial therapy.

The patient was consulted by an ophthalmologist (23.08.2019). Was diagnosed with stage I retinal angiopathy. Hyperplasia of the lacrimal glands. Partial ptosis of the upper eyelid of the left eye.

From 23.08.2019, against the background of the therapy with prednisolone, the patient began to notice an improvement in the vision of the left eye, an improvement in general well-being.


The patient underwent surgical treatment: maxillary ethmoidotomy on the left on 08/06/2019 and antromastoidotomy on the right of 08/16/2019. intramuscularly, loratadine inside, nasal cavity toilet, nasal ointment on gauze trailer, right ear toilet, dioxidine in the right ear in drops and on gauze trailer.

On August 29, 2019, the patient was consulted by the head of the Department of Hospital and Polyclinic Therapy of the Kazan State Medical Academy, Professor R.G. Sayfutdinov. Considering a long history of the disease, the presence of a persistent, fibrosing nature of the lesion of the sinuses, a constant high ESR level of the blood (50 - 60 mm/h), the presence of positive dynamics against the background of hormone therapy, the diagnosis was made: Ig4 - associated disease (Mikulich’s disease)? The following were recommended: taking an Ig G4 test, taking prednisolone 30 mg per day (3 tablets in the morning, 2 tablets in the afternoon, 1 tablet in the evening), observation by an ophthalmologist, neurologist, ENT doctor.

The result of the patient’s analysis for Ig G4 from 01.09.2019g - 2.29 g/l (0.1 - 1.35 g/l).

The patient was given the final clinical diagnosis: Ig4 - associated disease (Mikulich’s disease). Exacerbation of bilateral chronic hyperplastic rhinosinusitis. Secondary rhinogenic meningitis. Ptosis and reactive edema of the upper eyelid of the left eye. Amblyopia. Retinal angiopathy on the left. Right-sided exudative otitis media, sluggish mastoiditis on the right. Stress hyperglycemia. Anemia is multifactorial, mild. Exacerbation of chronic bronchitis.

On September 2, 2019, the patient was discharged with improvement under the outpatient supervision of a general practitioner, oculist, otolaryngologist, neurologist at the place of residence. The patient was advised to avoid hypothermia and water entering the ears. Treatment of the seam in the behind-the-ear region on the right with iodine solution 2 times a day for 10 days. Peach oil in the nose.

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3 - 4 drops, 3 - 4 times a day, for 1 month. Prednisolone 30 mg per day (3 tablets in the morning, 2 tablets in the afternoon, 1 tablet in the evening).

On September 12, 2019, the patient was consulted by a doctor in connection with a worsening of his condition due to self-withdrawal of prednisolone. From 09/10/2019 to 09/12/2019, the patient stopped taking prednisone due to the fact that he could not buy it at the pharmacy. After the withdrawal of prednisolone, I felt a deterioration in health, an increase in temperature to 37.8°C, An increase in ESR up to 90 mm in hour (09/12/2019). The patient was recommended to take metipred in an equivalent dose, consultation with an ophthalmologist.

12.09.12 the patient was consulted by an ophthalmologist. Conclusion: OU-retinal angiopathy. OC is simple myopic astigmatism.

09/23/2019 the patient came for a second appointment. On the background of the therapy, the patient’s well-being became good, the temperature returned to normal, and his vision recovered by 95%.

Conclusion

Thus, Mikulich’s disease is a rare chronic disease characterized by a slowly progressive symmetric painless enlargement of the lacrimal and salivary glands, an increased concentration of immunoglobulins of the IgG4 subclass, and infiltration of tissues of various organs by IgG4 plasma cells. The etiology of the disease has not been established [1-3].

The given clinical case demonstrates an example of a confirmed IgG4 associated disease (Mikulich’s disease).

Conflict of Interest

There is no financial interest or conflict of interest.

Bibliography


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