A case of isolated IgG4-related lung disease in a teenager

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IgG4-related disease (IgG4-RD) is a rare immune-mediated fibroinflammatory disease that is characterized by the occurrence of nodules in one or more organs and proceeds in most patients with the elevated levels of IgG4 in serum and/or in the tissues of the affected organs. The majority of patients are elderly men, and the disease in most cases has a slowly progressing systemic course. The cases of isolated IgG4-related injury to the viscera, which are much less common than the systemic type of the disease, are a very difficult differential diagnosis, and biopsy of these organs is associated with technical difficulties and poses a threat to the patient's health. The paper describes just such a case. It is interesting from several points of view: firstly, a rare site (solitary pulmonary nodular lesion); secondly, clinical and laboratory features (childhood onset, no immunological abnormalities – both higher serum IgG4 levels and lower complement components).

Clinicians should remember that IgG4-RD does not always have a systemic course and characteristic serological markers. In these cases, histological verification of the diagnosis is of particular importance. If the histological pattern of a fibroinflammatory pseudotumor is identified, especially in the presence of multiple nodules, IgG4-RD should always be included in the differential diagnosis.

Keywords: *IgG4-related disease; IgG4-related lung disease; clinical case.*

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IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory disease, characterized by tumor-like lesions formation in one or multiple organs. The majority of patients have IgG4 hypersecretion in the serum or in the affected tissue. The most frequently affected organs are: major salivary glands, orbits, lacrimal glands, pancreas and biliary tract (autoimmune pancreatitis type 1 and IgG4-related sclerosing cholangitis), retroperitoneum, but almost any organ can be involved [1,2]. The disease has a chronic course with slow progression, lacking constitutional symptoms, and usually good response to immunosuppressive treatment. 60–90% of patients have a systemic disease at the moment of diagnostics, but rarely isolated IgG4-related lesions are detected [3–6]. Isolated lesions are difficult for diagnostics and require a vast differential diagnosis. Pathomorphological examination is a core stone of the diagnosis of IgG4-RD, but when only pancreas, lungs or retroperitoneum are affected biopsy can be difficult and dangerous to perform. On the other side biopsy of an isolated lesion plays a crucial role, it allows reliable differential diagnostics first of all with malignancies..

Lungs are affected in 30–50% of patients with IgG4-RD and have quite heterogeneous patterns [3,4,7–10]. D.Inoue et al. [11] proposed 4 main radiologic patterns of IgG4-related lung disease: 1) solid nodular type 2) round-shaped ground-glass opacity type 3) alveolar interstitial type and 4) bronchovascular type. Later other patterns like lung cavities, pleural thickening and/or effusion and pathognomic feature – paravertebral soft tissue bands, were described [10,12.13]. Different patterns can be combined in one patient making diagnostics more complicated [14]. Pathomorphologic features of the IgG4-related lung lesions are also unique: storiform fibrosis may be not prominent, phlebitis can be not obliterative, there can be small vessel artheriolitis and neutrophilic addition in the infiltrate [15]. Destructive vasculitis, prominent neutrophilic infiltrate, granulomas are usually exclude diagnosis of IgG4-RD [15]. Here we describe a rare case of isolated IgG4-related lung disease in an adolescent.

A 16-year old male patient was transferred to the X-ray and then thoracic computer tomography (CT) after positive skin tuberculosis test results (d=12 mm). On the chest X-ray multiple solid nodules in both lungs were found (picture 1). On CT: in the S1-S2 and S6 of the left lung there was a 1,5 cm lesion, in S7-S8 of the right lung multiple lesions with irregular margins up to 5,5 cm in diameter with calcification were found. All lesions were contrast positive (picture 2).

The patients was admitted to the surgery department to perform differential diagnosis. Tne new skin tuberculosis test, sputum and bronchial lavage culture and PCR were negative for tuberculosis. On bronhoscopy a total blockade of B8b bronchus was detected due to compression. There were no malignant cells in the bronchial lavage. A surgical resection of the right lung was performed. On pathology a dence fibrosis with crossing bundles and spindled cells with prominent lymphoid infiltration was found – the picture of lung pseudotumor or inflammatory myofibroblastic tumor. Due to unsurtain pathologic answer a second surgery on the left lung was performed. Pathologic picture in the left lung tissue was the same. Both biopses were revised in the expert institution and immunohystochemical stains were performed. In both lesions there were dense fibrosis, obliterative phlebitis, arteriitis, dense lymphoplasmatic infiltrate with IgG4 hypersecretion (150–350 IgG4-positive cells per hpf), no ALK secretion or κ/λ restriction – the picture of IgG4-RD (picture 3).

The patient was admitted ton the Institute of rheumatology. At admission patient is nomostenic, with proper nutrion (BMI 22,8 kg/sqm). Auscultation in interscapular region showed sibilant crepitant wheezes with no patological results in other organs and systems. In CBC, general analysis of urine and biochemical parameters of blood, aslo no deviations were detected. In the blood immunological analysis, the CRP level is 0.5 mg / L (normal up to 5 mg / L), the level of all immunoglobulins, including IgG4 and IgE, the level of complement components were within the normal range, ANCA screen is negative. To identify other possible foci of active disease, the patient underwent 18F-FDG-PET / CT with additional IV contrast, according to which no foci of active accumulation were noted. Thus, the diagnosis was formulated as follows: IgG4-RD, probable (IgG4-related lung disease), remission (after surgical treatment). It was decided to adopt a «watchful waiting» approach. The patient is observed at the Institute of Rheumatology annually (to date for two years), there is no data pointing to recurrence of the disease.

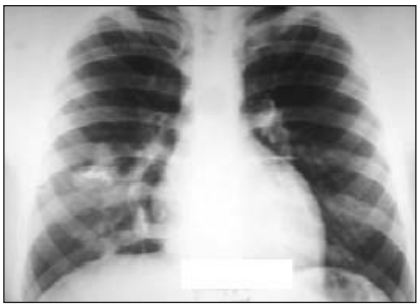

Fig. 1. *Chest X-ray in Patient R. aged 16 years*

Discussion. IgG4-C3 is a systemic fibroinflammatory disease in which one or more organs are affected synchronously or metachronously. The true frequency of this disease is not known; according to some Japanese researchers, it amounts to approximately 4.6: 10,000 of the population [16]. It is considered that older men are primarily affected by this disease, which is particularly true for IgG4-related lung disease [1,10]. Despite the fact that in recent years the awareness of physicians in Russia about the existence of this pathology has been growing, it still remains insufficient, especially outside large expert medical centers, which leads to late diagnosis and diagnosis errors. Cases of isolated IgG4-related damage to internal organs, which are much less common than the systemic variant of the disease, seem very difficult for differential diagnosis, and biopsy of these organs is associated with technical difficulties and pose a threat to the patient's health. We give a description of just such a case. This case is interesting from several points of view. Firstly, rare localization: isolated nodular lesion of the lungs. Secondly, by clinical and laboratory features: debut in childhood, the absence of any immunological abnormalities (both an increase in serum IgG4 and a decrease in the level of complement components). Probably, it was the presence of these features that made pulmonologists think first of all about a specific lung lesion and be wary of the TnonspecificУ nature of the changes according to lung biopsy, which led to unreasonable repeated surgical intervention.

Diagnostic criteria for IgG4-associated lung disease were proposed by S. Matsui et al. in 2016 [17], they are based on universal diagnostic criteria of IgG-RD H. Umehara et al. [18]. The given case meets the criteria for the probable IgG4-RD according to Umehara criteria and a reliable diagnosis of IgG4-related lung disease according to the organ-specific Matsui criteria, as there is histological and immunohistochemical confirmation of the diagnosis. In any case, the terminological subtleties should not affect the choice of treatment. According to existing guidelines for the treatment of IgG4-RD, treatment is required in the presence of an active disease of any location [19]. However, in the case we described, after FDG-PET / CT, it was decided to refrain from any therapy due to the lack of metabolically active tissue in the lungs. The therapeutic intervention, of course, is potentially more successful when the effects of lymphoplasmacytic infiltration rather than fibrosis are more pronounced in the affected organ, and PET / CT according to many researchers is a sensitive tool for assessing the severity of the inflammatory component in the organ and predicting the degree of response to therapy [20]. IgG4-RD responds well to immunosuppressive therapy, but is prone to frequent relapses, both in the same organ and beyond. The pathogenesis of the disease is still unknown, therefore, it is impossible to predict whether a relapse is going to occur, in which organ it is going to occur, and/or whether the disease acquires a systemic course. At the same time, cases of prolonged remission are known for many years after surgical removal of IgG-RD foci. To date, watchful waiting in relation to this patient is fully justified, there are no signs of disease progression.

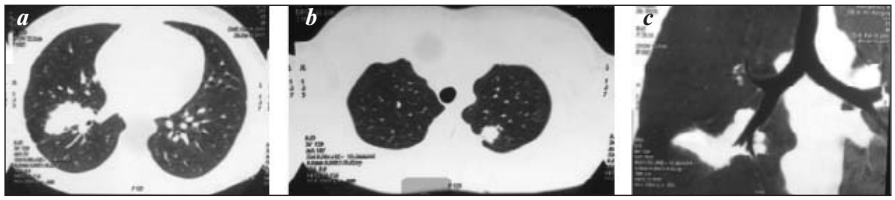

Fig. 2. *Chest MSCT in Patient R. aged 16 years: (a–c) – multiple nodules in both lungs*

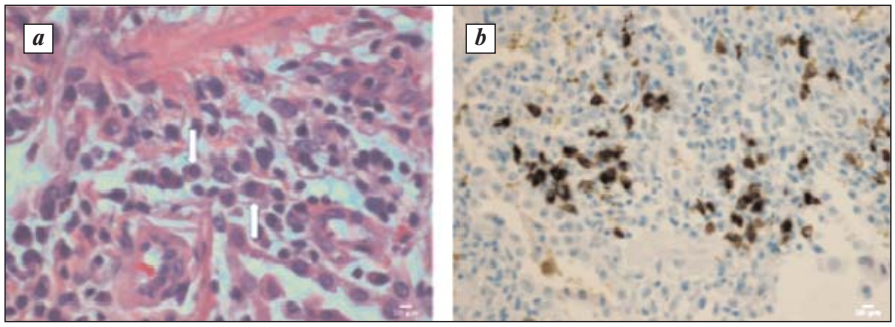

Fig. 3. *Examination of a lung biopsy specimen from Patient R. aged 16 years: a – histological study reveals a large number of plasma cells in the infiltrate (hematoxylin and eosin staining, ×400); b – immunohistochemical study identifies a large number of IgG4-secreting cells (immunoperoxidase staining method, ×400)*

Summing up: clinicians should remember that IgG4-RD does not always have a systemic course and characteristic serological markers. In these cases, histological verification of the diagnosis is of particular importance. When obtaining a histological picture of the fibroinflammatory «pseudotumor», especially in the presence of multiple nodular formations, IgG4-RD should always be included in the differential diagnosis analysis.

REFERENCES

1. Stone JH, Zen Y, Deshpande V, et al. IgG4-related disease. *New Engl J Med*. 2012;366(6):539-51. doi: 10.1056/NEJMra1104650
2. Kamisawa T, Zen Y, Pillai S, et al. IgG4-related disease. *Lancet*. 2015 Apr 11; 385(9976):1460-71. doi: 10.1016/S0140-6736(14)60720-0
3. Сокол ЕВ, Васильев ВИ, Пальшина СГ и др. Клинико-лабораторная характеристика IgG4-связанного заболевания и алгоритм его диагностики. Терапевтический архив. 2019;91(5):40-8. doi: 10.26442/00403660.2019.05.000236 [Sokol EV, Vasilyev VI, Palshina SG, et al. Clinical and laboratory characteristics of IgG4-realated disease and its diagnostic algorithm. *Terapevticheskiy Arkhiv = Therapeutic Archive*. 2019;91(5):40-8. doi: 10.26442/00403660.2019.05.000236 (In Russ.)].
4. Wallace ZS, Deshpande V, Mattoo H, et al. IgG4-Related Disease: Clinical and Laboratory Features in One Hundred Twenty-Five Patients. *Arthritis Rheum*. 2015 Sep;67(9):2466-75. doi: 10.1002/art.39205
5. Inoue D, Yoshida K, Yoneda N, et al. IgG4-related disease: dataset of 235 consecutive patients. *Medicine (Baltimore)*. 2015 Apr; 94(15):e680. doi: 10.1097/MD.0000000000000680
6. Chen H, Lin W, Wang Q, et al. IgG4-related disease in a Chinese cohort: a prospective study. *Scand J Rheumatol*. 2014; 43(1):70-4. doi: 10.3109/03009742.2013.822094
7. Hirano K, Kawaba T, Komatsu Y, et al. High-rate pulmonary involvement in autoimmune pancreatitis. *Int Med J*. 2006;36(1):58-61. doi: 10.1111/j.1445-5994.2006.01009.x
8. Matsui S, Taki H, Shinoda K, et al. Respiratory involvement in IgG4-related Mikulicz's disease. *Mod Rheumatol*. 2012 Feb;22(1):31-9. doi: 10.3109/s10165-011-0504-x
9. Yi ES, Sekiguchi H, Peikert T, et al. Pathologic manifestations of Immunoglobulin (Ig) G4-related lung disease. *Semin Diagn Pathol*. 2012 Nov;29(4):219-25. doi: 10.1053/j.semdp.2012.07.002
10. Wallace ZS, Perugino C, Matza M, et al. Immunoglobulin G4-related disease. *Clin Chest Med*. 2019;40(3):583-97. doi: 10.1016/j.ccm.2019.05.005
11. Inoue D, Zen Y, Abo H, et al. Immunoglobulin G4-related lung disease: CT findings with pathologic correlations. *Radiology*. 2009 Apr;251(1):260-70. doi: 10.1148/radiol.2511080965
12. Jinnur PK, Yi ES, Ryu JH, et al. Cavitating lung disease: a novel presentation of IgG4-related disease. *Am J Case Rep*. 2015 Jul 21;16:478-82. doi: 10.12659/AJCR.894015
13. Kasashima S, Kawashima A, Ozaki S, et al. Clinicopathological features of immunoglobulin G4-related pleural lesions and diagnostic utility of pleural effusion cytology. *Cytopathology*. 2019 May;30(3): 285-94. doi: 10.1111/cyt.12641
14. Matsui S, Hebisawa A, Sakai F, et al. Immunoglobulin G4-related lung disease: clinicoradiological and pathological features. *Respirology*. 2013 Apr;18(3):480-7. doi: 10.1111/resp.12016
15. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol*. 2012 Sep; 25(9):1181-92.
16. Kanno A, Masamune A, Okazaki K, et al. Nationwide epidemiological survey of autoimmune pancreatitis in Japan in 2011. *Pancreas*. 2015 May;44(4):535-9. doi: 10.1097/MPA.0000000000000325
17. Matsui S, Yamamoto H, Minamoto S, et al. Proposed diagnostic criteria for IgG4-related respiratory disease. *Respir Investigat*. 2016;54(2):130-2. doi: 10.1016/j.resinv.2015.09.002
18. Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol*. 2012 Feb;22(1):21-30. doi: 10.3109/s10165-011-0571-z
19. Khosroshahi A, Wallace ZS, Crowe JL, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheum*. 2015 Jul;67(7):1688-99. doi: 10.1002/art.39132
20. Zhang J, Chen H, Ma Y, et al. Characterizing IgG4-related disease with 18F-FDG PET/CT: a prospective cohort study. *Eur J Nucl Med Mol Imaging*. 2014 Aug;41(8):1624-34. doi: 10.1007/s00259-014-2729-3

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Conflict of Interest Statement

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