Multi-organ Involvement in Refractory IgG4-related Disease
Multiorganbeteiligung bei refraktärer IgG4-assoziierter Erkankung

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Key words
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- Multi-organ involvement
- Rituximab
- Refractory disease
- IRD

Abstract
IgG4-related disease (IRD) is a type of lymphoplasmacytic disease with multi-organ involvement. It is characterized by elevation of serum IgG4 levels and tissue infiltration of IgG4-positive plasma cells. Autoimmune pancreatitis, sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis and lymphadenopathy make up its main clinical manifestations, but almost any organ can be involved. The present difficult case was encountered in our hospital. The gentleman involved was middle-aged male of Indian heritage. He presented with a constellation of interstitial pneumonitis, periaortitis, pansinusitis, nephritis, prostatitis, dacryoadenitis and otitis media. Unexpectedly, multiple auto-antibody serologies measured at different intervals including serum IgG4 were all negative. This complex presentation was eventually diagnosed as IRD, namely through the histopathological findings demonstrating evidence of IgG4+ cells on immunohistochemical staining. The patient was non-responsive to high-dose steroid therapy and failed to improve on cyclophosphamide treatment also. Eventually, better disease control was achieved with the monoclonal anti-CD20 antibody rituximab. To the best of our knowledge, this is the first case report of a patient presenting with 7 different organ manifestations in a biopsy-confirmed IRD. Serial CT and PET/CT scans were used throughout this case to monitor the degree of organ involvement, disease remission and response to treatment.

Zusammenfassung

Introduction
IgG4-related disease (IRD) is a disorder characterized by sclerosis and infiltration of organs by IgG4-positive plasma cells. The disease may be complicated by a variety of extra-pancreatic lesions [1,2]. Possible manifestations include retroperitoneal fibrosis, dacroïdadenitis, sclerosing sialadenitis, thyroiditis, pneumonitis, pancreatitis, sclerosing cholangitis, tubulointerstitial nephritis, prostatitis, and hypophysitis [3], but almost any organ can be involved. The concept of a systemic IgG4-disease was introduced by Kamisawa et al. [4], who showed that patients with autoimmune...
pancreatitis (AIP) had extensive IgG4+ plasma cell infiltrate in other organs. They proposed the term “IgG4-related systemic disease” to describe this condition. In order to confirm the diagnosis, no matter which organ is involved, careful histopathological evaluation of tissue biopsy, immunohistochemical staining for IgG4 and serum IgG4-levels are essential. Systemic corticosteroids have been proven to be effective in treatment, when the diagnosis is established [5]. This report illustrates a case of steroid refractory, multi-organ involvement of a biopsy-proven IRD.

Case Report

A 61-year-old Sri Lankan male, living in Germany for more than 20 years, was referred to us with a 1-month history of fatigue, weight loss of 10 kg, fever, hip pain, bloody nasal discharge and cough with bloody expectorator. One month after onset of symptoms, he was evaluated by his local physician for persistent fever, cough, fatigue, progressive weight loss and admitted to a local community hospital.

Physical examination revealed no abnormalities except for elevated temperature, weight loss of 10 kg within one month, basal crackles on lung auscultation and hip and buttock pain. Laboratory examination, showed normocytic anemia with hemoglobin of 12 g/dl, leucocytosis of 13.5 × 10³/ul, thrombocytosis of 534 × 10⁶/ul, erythrocyte sedimentation rate (ESR) of more than 80 mm/h and C-reactive protein (CRP) of 274 ml/L. Chest x-ray displayed pneumatic infiltrates in the left and right lower lung fields, therefore empiric antibiotic treatment was administered. A bone scintigraphy was unremarkable. CT brain and skull displayed features suggestive of sinusitis. A CT thorax described multiple abscesses up to 3.5 cm in diameter, perifocal infiltrates in both lungs and a 1.5 × 6 cm lesion surrounding the infrarenal aorta. For further investigation a bronchoscopy was performed. The bronchoalveolar lavage revealed enterococci and pseudomonas aeruginosa. Antibiotic therapy was adapted based on the microbiology findings. Thereafter the fever subsided. However due to the ongoing constitutional symptoms and elevated inflammatory markers, the patient was then referred to a tertiary care center.

On physical examination at this institution, the patient appeared chronically ill, but in no acute distress. He was alert, oriented and had an appropriate affect. He was febrile with a temperature of 38.5 °C. Blood pressure was equal in both arms and pulse was regular at 60 beats per min. Skin examination was unremarkable. On auscultation of the lungs bi-basal wet crackles were audible. Vascular system as well as musculoskeletal examination were both normal. In order to investigate the suspicious pulmonary lesions, a needle biopsy was taken which revealed a chronic inflammatory process with numerous macrophages and focally increased eosinophils. Subsequently a wedge resection of one of the suspicious lesions was performed. The result of the wedge resection displayed a perifocal vasculitis. After microbiological examination tuberculosis and fungal infections as differentials were both excluded. The findings of lymphoplasmacytic inflammation, associated with storiform sclerosis and obliterative phlebitis were judged as suggestive of IRD (Fig. 1a), immunostaining for CD138 and IgG4 was performed, which displayed an increased number of IgG4 positive plasma cells with a IgG4:IgG ratio of 0.5. IgG4-plasma cells formed small aggregates and were prominent around obliterated veins (Fig. 1b, c).

Further serological examinations revealed a positive rheumatoid factor of 24.41E/ml (<20E/ml), an antinuclear antibody (ANA) of 1:100, positive anti-neutrophil cytoplasmatic antibodies C/PR3 (C-ANCA) of 6.7 U/ml (0–6 U/ml), slightly elevated IgG1 and IgG3-levels, with normal IgG2 and IgG4 levels. Other serologies such as cryoglobulins, total complement level, fungal serology, hepatitis serology, Lyme disease and syphilis were all negative. Based on the findings of the lung biopsy, a diagnosis of IgG4-related disease was made and the treatment with high dose intravenous corticosteroids was initiated. Initially, this led to an improvement of the clinical status and a decrease of the periaortal mass on abdominal ultrasonography. During the clinical course however, the general condition of the patient deteriorated and he began to vomit faecal matter. A further CT evaluation roughly one week after admission showed signs of a small bowel ileus, no increase in size of the periaortic mass, accompanied by nodular renal cortical changes and acute panniculitis.

Due to ongoing small bowel obstruction and failure to improve with conventional therapy, the patient was referred to the surgeons for exploratory laparotomy. In the operating theatre the mechanic ileus proved to be caused by an adhesion of small bowels to omentum majus. During the tapering of the steroids, the clinical state of the patient worsened, along with a rise of inflammatory markers. Before initiating further immunosuppressive therapy we performed a fluorodeoxyglucose positron emission tomography scan (FDG PET/CT) (Fig. 2).

The periaortal mass displayed little FDG-uptake, progression of the pulmonary lesions and multiple FDG-positive lesions in both kidneys. Furthermore panniculitis and prostatitis were detected. Due to the rise of inflammatory markers in combination with the PET-CT findings demonstrating multiorgan involvement, we have decided to start cyclophosphamide
immunosuppressive therapy with 800 mg intravenously. A follow-up CT one month later revealed pulmonary consolidations with increasing cavitations, partly regressing pansinusitis, a new swelling of the lacrimal glands, along with a stable soft tissue cuff around the abdominal aorta, representing the periaortitis. The hypodense renal lesions on both sides have increased in size. In addition a consolidation of the mastoid cells and the tympanic cavity on the left side was described (Fig. 3).

The cyclophosphamide therapy was continued in 3 weekly intervals. At the next clinical assessment, 3 months later, the patient complained of worsening ocular swelling, accompanied by pain and increased lacrimation. Moreover, his hearing has progressively worsened. The follow-up CT demonstrated regressing pansinusitis, swelling of the lacrimal glands and the tympanic cavity bilaterally. The previously described bilateral pulmonary cavitations have regressed. In addition a new pulmonary lesion in the left lower lobe was noted. The renal lesions were stable.

Due to consolidation of the tympanic cavity, the patient suffered from progressive hearing loss accompanied by ear pain. In total the patient has received 5 infusions of cyclophosphamide in a dosage of 800 mg in 3 weekly intervals, with a cumulative dosage of 4 g. Regarding the radiological follow-up assessments, especially the most recent one, where multorgan disease activity was still observed, a more intensive approach/therapy was indicated. Subsequently the patient received rituximab, a chimeric monoclonal anti-CD 20 antibody. He tolerated the treatment well. Following 12 months of treatment and during disease activity staging, a repeat PET/CT was done which showed regressing, but still partially active inflammatory renal uptake and a low residual inflammatory activity in the area of the paraaortal mass, which regressed in size (Fig. 4).

**Discussion**

Based on our findings and the current literature this patient was diagnosed with a form of multorgan IRD, resulting from the excessive infiltration of polyclonal IgG4-positive plasma cells into many organs. Our patient was 61 years old and had a history of asthma. The typical age at presentation is in the mid 50s to early 60s and patients frequently have a history of allergic rhinitis or bronchial asthma [6]. Symptoms of bronchial asthma can precede an IRD [7, 8]. Laboratory examinations revealed elevated inflammatory markers, a hypergammaglobulinemia and normal range IgG4-levels. In the majority of patients, hypergammaglobulinemia and increased serum levels of IgG, particularly IgG4 was found [1, 9]. In our patient IgG4-levels were in the normal range during admissions and at follow-up visits. The immunological examinations showed slightly elevated levels of rheumatoid factor, antinuclear antibodies and anti-neutrophil cytoplasmic antibodies. Patients with this disease may have an elevated rheumatoid factor, as well as elevated autoantibodies [10]. Although the pancreas is the most commonly affected organ, the presence of AIP is not obligatory [11]. According to Kamisawa et al. [12] males seem to be affected more commonly. In men the disease seems to be more severe and it is likely to include pancreatic and renal involvement [6]. In our patient the first organs being involved were the lungs and the sinuses. The cranium and the thorax CT examinations showed consolidations in the lungs, partly melting, a pansinusitis and a 6 cm long lesion, surrounding the infrarenal aorta. The changes observed in IRD are often non-specific and tissue biopsy of the involved organ is needed (Fig. 4).
mandatory. It is of uttermost importance, due to the patchy distribution of the disease to get sufficient biopsy material, a small tissue sample, for example a core needle biopsy might miss the diseased tissue [13]. This could be observed in our patient, where the first needle biopsy revealed unspecific inflammatory changes. Subsequently a wedge resection of a peripheral pulmonary lesion was taken, where firstly a chronic, plasma cell-rich inflammation with sclerosis was observed. This finding led to the high suspicion of an IRD, subsequently an IgG4-stain was performed, which confirmed the diagnosis. The first CT described a pannusinitis, multiple pulmonary abscesses, partly melting and pulmonary perifocal infiltrates, accompanied by an infraenal periaortic lesion. The following CT done to assess the small bowel ileus showed a slight decrease of the periaortic mass under treatment with corticosteroids. The next examination done was a PET/CT. Drieskens et al. [14] concluded that PET/CT can play an important role in establishing the diagnosis and the sites of involvement and in evaluating the activity and patient response to corticoid therapy in IRD. The latest publication from Nakatami et al. [15] states that PET/CT has a valuable role in staging the extent of disease, guiding biopsy, and monitoring response to treatment. The first PET/CT of our patient displayed, as outlined in detail above, involvement of the sinuses, the lungs, the prostate, the aorta and the kidneys. There are 2 cases published where involvement of the sinuses in IRD were described [16,17]. Pulmonary IRD may appear as solitary or multiple lung nodules, or consolidation and hiliar lymphadenopathy [18]. In our case multiple lung nodules could be observed. During the clinical course they changed morphology and became cavernous. Several cases of IgG4-triggered prostatitis are described until now [19,20]. In addition to FDG-uptake, our patient complained of lower urinary tract symptoms, which improved after steroid therapy. Furthermore the PET/CT displayed a soft tissue cuff surrounding the abdominal aorta, thought of as periaortitis. So far there are 6 cases IgG-related aortitis published [21–25]. Concerning the location of the inflammatory process, a remarkable variability was observed. In 3 of the 6 cases there was predominance for adventitial inflammation, like observed in our patient. The next organ which showed FDG-uptake were the kidneys, where in the renal cortex numerous hypodense lesions were described. The first description of IgG4-related kidney diseases in association with autoimmune pancreatitis was published in the year 2004 by Japanese authors [26,27]. To date, more than 40 cases have been reported as IgG4-related kidney disease exhibiting tubulo-interstitial nephritis (TIN). Deteriorated renal function was confirmed in approximately two thirds of patients, while the remainder showed no renal dysfunction despite the progression of TIN [28]. Our patient showed no changes pointing towards renal dysfunction, nevertheless there seems to be an active IgG4-mediated inflammation observed by PET/CT. The CT done previously already observed renal cortical changes. IgG4-related kidney disease can be noted by radiological changes observed in CT scanning [29–31]. PET/CT visualizes the pseudo-inflammatory lesions seen in renal involvement. Lee et al. [32] examined 17 patients, where FDG uptake was seen in kidney and salivary glands as well as in pancreas of patients suffering from AIP. The next diagnostic imaging, a CT examination done one month later displayed pulmonary consolidations with increasing cavitations, new findings were a swelling of the lacrimal glands (dacrroachdenitis) on both sides and a consolidation of the mastoid cells and the tympanic cavity on the left side (otitis media). IRD commonly affects the lacrimal glands and periorbital soft tissue and these were the initial sites involved by this disease apart from the pancreas [18]. Unilateral or bilateral, painless chronic orbital swellings with or without visual impairment or symptoms of ‘dry eyes’ are described [33,34]. Extensive involvement of orbital soft tissue and sclerosis may lead to markedly decreased visual acuity and occasionally cause optic nerve atrophy and blindness [34]. The consolidation of the mastoid cells and the tympanic cavity on the left side were interpreted as inflammatory changes. Cho et al. [35] described a case of IgG4-related otitis media. It is not uncommon that the organ manifestations change during the course of an IRD, therefore close monitoring is necessary in order not to miss new sites of inflammation. Kamisawa et al. [36] described in a series 2 patients who suffered from sclerosing sialadenitis and developed AIP only during follow-up. After cyclophosphamide and corticosteroids failed to achieve disease control, we have escalated the treatment to the anti-CD-20 antibody rituximab. Until now there are 2 case reports of altogether 14 patients [37,38] treated with rituximab, where rapid disease control with decrease of lymphoplasmacytic organ infiltration and serum IgG4-concentrations were achieved. Similar to the results described by these authors, our patient reacted well to the rituximab therapy and achieved nearly total remission. The authors hypothesize that rituximab achieves its effects by disrupting the normal differentiation of IgG4-bearing B lymphocytes into plasma cells. The repeat PET/CT documented the good response, as there was only little residual activity observed in the kidney and the periaortal mass.

**Conclusion**

This is to date the first case report where 7 organ manifestations of an IRD were observed in one patient. Our patient suffered from interstitial pneumonitis, periaortitis, pannusinitis, nephritis, prostatitis, dacrroachdenitis and otitis media. This case is a good example of how disease manifestations can develop and change during the course of an IRD; some respond well to therapy and on other occasions new manifestations of this illness may develop during treatment. It is necessary to obtain a proper organ biopsy OR sufficient tissue material (no fine needle biopsy) for histological and immunological analysis as involvement may be patchy. It is not mandatory to find elevated IgG4-serum levels in a patient suffering from IRD. The PET/CT is a valuable tool in diagnosing the diverse organ manifestations, staging and follow-up response to therapy. Last but not least, this case underlines the fact, that patients refractory to steroids and cyclophosphamide respond well to the anti-CD20 antibody rituximab.

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References


