

IgG4 related disease in elderly: a case report

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IgG4-related systemic disease (IgG4-RSD) is an emerging autoimmune disorder that may affect several organs, with signs of organ fibrosis, storiform masses for histopathological plasmacellular infiltration and plasmatic elevation of IgG4. This clinical condition frequently occurs in the sixth decade and may be considered an autoimmunity of the elderly; the disease may have a smouldering course with frequent misdiagnosis for the co-occurrence of comorbidity and clinical complexity.

The present case report describes the clinical case of an 81 years old woman admitted to the geriatric ward for remittent fever and functional decline. The past clinical history reported an isolated CT scan suggestive of retroperitoneal fibrosis of unknown origin with and a drug regimen that included chronic corticosteroids (prednisone 5 mg oad). The in hospital diagnostic workout demonstrated the presence of a thoracic aneurysm. Several possible diagnoses among inflammatory, autoimmune (connective tissue disease, vasculitis, sarcoidosis, amyloidosis), infectious (mycotic) or neoplastic conditions were ruled out, as well as any drug association with higher risk of retroperitoneal fibrosis.

Thus, the clinical hypothesis of an IgG4 chronic periaortitis was formulated due to the co-occurrence of all the three major components: the presence of a retroperitoneal fibrosis, IgG4 related abdominal aortitis and peryaneurysmal fibrosis. Patient's comorbidity did not allow performing the histological analysis. The present clinical case is original and adds knowledge to the 76 cases of thoracic aortitis due to IgG4 systemic disease out of the 3482 cases of disease reported so far. Further clinical investigation is needed to provide a homogeneous diagnostic workout for tailored early therapeutic intervention on the single geriatric patient. Moreover, a growing awareness of the disease is needed, especially in geriatrics, to providing a better standard of care and to improving the disease clinical knowledge and management.

Key words: Older adults, Autoimmunity, Disease

INTRODUCTION

IgG4-related systemic disease (IgG4-RSD) is a sub acute autoimmune systemic disorder, characterized by the lymphoplasmatic infiltration of different organs and tissues, leading to fibrosis. The first discovery was in 2001¹, when the sclerosing autoimmune pancreatic disease was associated to extra pancreatic sites. The most frequently involved sites include bile ducts and

gallbladder, liver, salivary glands, and kidneys, generally mimicking a neoplasia. The cardinal features are histological IgG4 expressing cells, organs fibrosis and potential elevation of serum IgG4²⁻⁴. Interestingly, the mean age at diagnosis is approximately 60 years, with men prevalence (8:3); it indicates an epidemiologic trend in older adults⁵. The disease pathogenesis remains largely unclear; so far, there is increasing evidence of a Th2-driven immune response, that induces

■ Received: November 25, 2015 - Accepted: June 17, 2016

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IgG4 production, associated to innate immunity activation (toll-like receptors and monocytes and basophiles) and potentially mediated by infectious agents.

The diagnosis may be challenging when unusual organs are involved or pre-existing comorbidity is present, delaying the early therapeutic interventions. The under diagnosis is particularly frequent in elderly subjects, due to the co-occurrence of multimorbidity, polypharmacy and clinical complexity.

We reported a clinical case of IgG4-related systemic disease in an oldest old woman. The clinical case is original and outlined the difficulty in the diagnostic workout of this elderly autoimmune disease due to the oldest old patient's clinical phenotype.

CASE REPORT

An old woman of 85 years was admitted to our geriatric ward (IRCCS University Hospital, San Martino Genoa, Italy) for remittent fever and functional decline. Her clinical history included arterial hypertension, osteoporosis and a polypharmacy (ramipril 5 mg oad, alendronate 70 mg oaw, calcium/Vit. D oral supplementation of 1000 mg/800 UI oad and prednisone 5 mg oad). The steroid therapy was introduced in 2009 when the patient had suffered from an abdominal colic; a previous CT scan described a storiform fibrous mass, suggestive of retroperitoneal fibrosis of unknown origin.

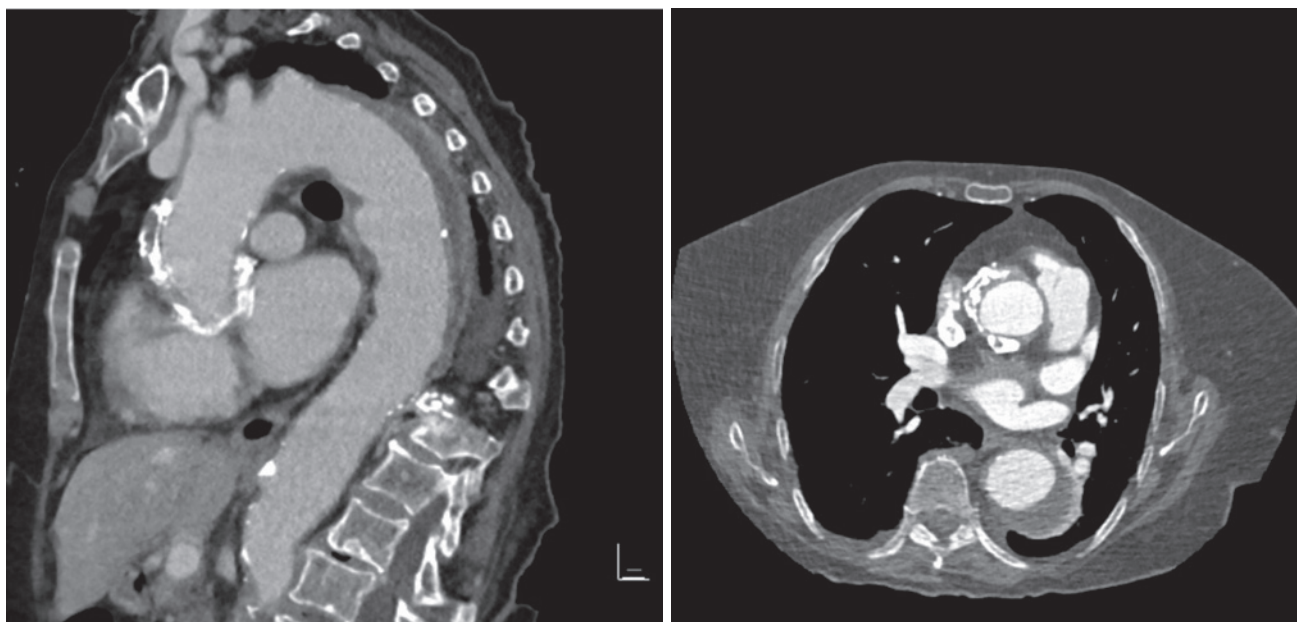
At the time of in hospital admission, patient's clinical

examination was non informative, other than a mild low abdomen tenderness. Laboratory tests, showed a mild increase of inflammatory plasmatic markers (erythrocyte sedimentation rate, ERS 30 mm/h; C-reactive protein, CPR 10 mg/l).

The comprehensive geriatric assessment showed a functional decline (ADL 3/6, IADL 3/8), a malnutrition risk (MNA 17/30), a mild cognitive impairment (MMSE 25/30) and a moderate comorbidity status (CIRS 4/13). The chest X-ray showed an upper mediastinum enlargement; a thorax-abdomen contrast enhanced CT and PET-CT scans showed periaortic inflammatory fibrosis, the aneurysm of the descending aorta (max AP diameter 55 X44 mm) and of the anony artery (max AP diameter 23 mm). A hydronephrosis, due to retroperitoneal fibrosis, that encapsulated the ureter was also observed (Fig. 1-2). The differential diagnosis was then formulated. The patient did not show any clinical sign suggestive of either polymyalgia rheumatica or Horton's aortitis: muscles and shoulders did not show any sign of stiffness or pain. The patient did not suffer from headache, vision difficulties, jaw pain, scalp tenderness and /or temporal artery tenderness or decreased pulsation, suggestive of gigantocellular aortitis.

No medium vessel vasculitis sign was demonstrated, including myalgias, erythema or maculopapular rash.

Moreover, no small vessel vasculitis sign was observed, including polyneuropathy, migratory or transient pulmonary opacities, purpura or organs bleeding. Sarcoidosis was also ruled out due to the absence of large lymph



Figures 1-2: TC and PET-TAC scans showed periaortic inflammatory fibrosis, the aneurysm of the descending aort (max AP diameter 55 X 44 mm) and of the anony artery (max AP diameter 23 mm) and hydronephrosis due to retroperitoneal fibrosis.

nodes involvement, arthritis, rash or erythema nodosum and interstitial and fibrotic pulmonary disease. Systemic amyloidosis was excluded due to the absence of nephrotic syndrome, autonomic neuropathy with orthostatic hypotension. Additionally, anti-nuclear antibody, (ANA); anti-neutrophil cytoplasmic antibodies, (ANCA); extractable Nuclear Antigen Antibodies, (ENA); rheumatoid factor (RA test); angiotensin converting enzyme (ACE) resulted negative, excluding the autoimmunity hypothesis.

A serum infective panel including Syphilis test, viral, bacterial biological samples, micotic (1-3)- β -D-glucan and galactomannan blood test ruled out the infective/mycotic origin for the aneurysm. Specifically, the patients did not show any sign of bacteraemia and/or sepsis to support an adjacent aortic spreading from the infectious focus. An echocardiography ruled out the presence of infective endocarditis. No iatrogenic trauma or prosthetic arterial device was present to support a specific risk factor for mycotic aneurysms. No immunosuppression state was shown counting for opportunistic infections. The clinical hypothesis of neoplasia and or lymphoma was also clinically excluded. Any patient's drug associated with higher risk of retroperitoneal fibrosis was ruled out.

The clinical hypothesis of an IgG4 related systemic disease was formulated.

Serum levels of IgG4 were 135 mg/dl (reference values: 8-135 mg/dl) in spite of a long-term treatment with glucocorticoids⁶⁻⁷, that is known to blunt the IgG4 mediated response.

The patient fulfilled most of the current diagnostic criteria for IgG4-RSD, including a clinical presentation with fibrous, storiform masses, the plasmatic detection of IgG4³ 135 mg/dl and the histopathological mass plasmacellular infiltration⁴.

The patient's old age did not allow the performing of histology, for an unfavourable clinical benefit to risk ratio; in keeping with that, the diagnosis of a possible IgG4 – related disease was formulated.

In particular, among the wide spectrum of IgG4 disease presentation, a IgG4-chronic periaortitis diagnosis was formulated for the presence of all the three major components: a retroperitoneal fibrosis, IgG4 related abdominal aortitis and peryaneurysmal fibrosis.

Herein, the patient had an in hospital occurrence of *Clostridium difficile* colitis, which precluded the administration of immunosuppressants and the steroid therapy (prednisone 7.5 mg oad) was increased to provide the optimal therapeutic effect.

DISCUSSION

The present clinical case is original and adds knowledge to the 76 cases of thoracic aortitis due to IgG4

systemic disease out of the 3482 cases of disease reported so far^{5,8}.

IgG4-RD is not a truly new disease, as many single clinical conditions (e.g., Mikulicz disease, Kuttner tumour, Riedel thyroiditis, Ormond's disease), once considered as separate clinical entity, are now included under its clinical wide spectrum^{9,10}.

So far, IgG4 is a multisystem disorder with a mean of 2 organ involvement; the hepato pancreaticobiliary system is the most commonly involved apparatus, followed by the parotid salivary glands anatomical system¹¹.

Interestingly, accumulating evidence indicates that in nearly half the cases, retroperitoneal fibrosis may be among the first clinical manifestation of IgG4-RD⁹, partially overturning the rareness of the retroperitoneal fibrosis in the idiopathic form.

Male and female differed in their organ representation; male predominantly presented with periaortitis while women presented with sialodacryoadenitis¹², even if the reasons for differential organ expression in the two sexes is still unclear.

With regard to that, the present clinical case is original, referring to the IgG4 clinical presentation with chronic periaortitis in an oldest old woman.

In particular, the Ormond's disease, once recognized as isolated idiopathic disorder, is now classified within the disease grouping known as chronic periaortitis, including aortic abdominal aortitis and peryaneurysmal fibrosis.

The presentation of IgG4 chronic periaortitis can be aspecific and subtle as in the reported clinical case. Common symptoms are pain in the back, lower abdomen, hydronephrosis from ureteral involvement and storiform fibrosis of retroperitoneum, especially for long standing cases.

The diagnosis of chronic IgG4 aortitis was formulated with a level of possibility due to the lack of biopsy.

However, it is also important to note that even if the tissue biopsy is the gold standard for the diagnosis of IgG4 RS, there is increasing indication to supporting clinic pathological evidence to confirm the diagnosis. This statement is of key relevance when dealing with older and frail elderly subjects where a biopsy procedure may be of difficult performance.

Corticosteroids represent the first line treatment, but the conventional steroid sparing agents (azathioprine, mycophenolate mofetil and methotrexate) may achieve additional immunosuppression benefit, lacking prospective controlled studies to test their efficacy. The caveats to such therapeutic immunosuppressive interventions pose additional concerns when dealing with an oldest old and comorbid patient.

In this clinical case, low dose chronic steroids were initiated in 2009, inducing a clinical remission; it is known

that, low steroid dose treatment at initial treatment and low levels of serum IgG4 in cases with organ dysfunctions are associated to disease recurrence, as occurred in the clinical report¹³.

The IgG4 RS represents a challenge in geriatrics, even if the disease nomenclature has been standardized, consensus have been reached and effective treatments have been identified.

In particular, the epidemiology of the disease in the older adult population is largely unknown, because of the challenges in early recognition and treatment.

The disease multi organ involvement and storiform fibrotic masses presentation often arises concern for malignancies or may be underdiagnosed in elderly, due to the co-occurrence of multimorbidity and disease smouldering courses. For instance, many elderly patients, with elevated plasmatic creatinine and urea levels, associated to gastritis, chronic thyroiditis, recurrent cholangitis and chronic pancreatitis are erroneously attributed to multimorbidity and treated for the single organ clinical condition. Additionally, the presence of organ mass involvement, may be erroneously suspected of malignancy, initiating a patient's distressing and inconclusive oncological diagnostic workout.

From a pathogenetic view point, the ageing process is characterized by the immunosenescence¹⁴, that may boosts autoimmunity; the enhanced reactivity to self-antigens and the loss of tolerance, explaining both the general inflammation (inflammaging)¹⁵ and the rise of autoantibody (altered T- and B-cell functions, especially to the decrease in antibody affinity maturation) may constitute the pathogenetic background for it⁵. In addition, epigenetic changes associated to aging (DNA methylation, histone modifications, telomeres shortening) may also contribute to foster late onset autoimmune diseases in elderly.

IgG4-RD is a clinical issue of growing interest: to date, indeed, few studies have reported, analytically, the systemic involvement of the disease in larger cohorts of patients¹⁰.

Anyway, greater understanding of the immunopathology of IgG4 diseases and interactions between T cell different pathways will be of key relevance in dissecting the IgG4 disease pathogenesis.

Further, greater awareness of IgG4-RD mediated pathogenesis is needed, especially in geriatrics, and a multidisciplinary collaboration is warranted to provide evidence based results and to improve the appropriateness and accuracy of the clinical management of this emerging immune mediated disease of the older age.

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