SPECTRUM OF MANIFESTATIONS OF IGG4-RELATED DISEASE: A LITERATURE REVIEW

REVIEW ARTICLE

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ABSTRACT

IgG4-Related Disease is a plasma cell lymphoproliferative condition, associated with increased levels of IgG4 and infiltration of IgG4-positive cells in affected structures. Due to its broad spectrum of manifestations, there are still difficulties in its diagnosis. This study aims to highlight the main clinical manifestations that comprise its spectrum. It is an integrative, descriptive literature review with a qualitative approach, conducted in the databases Embase, PubMed, SCIELO, and Web of Science. Thirty-eight articles were included in this review. It is observed that IgG4-Related Disease has a variable clinical presentation, with reports in the literature of involvement in all organs and systems of the body. The most affected organs are the pancreas, ocular orbits, salivary, and lacrimal glands. It is noteworthy that this variety of manifestations results in different clinical repercussions, which can lead to complicated conditions due to the possibility of affecting vital organs.

Keywords: IgG4-RD, Autoimmunity, Immunoglobulin G.

1. INTRODUCTION

Immunoglobulins (Ig), also known as antibodies, are proteins synthesized by the immune system to provide protection to the organism. They can be divided into 5 classes: IgA, IgD, IgE, IgG, and IgM. Immunoglobulins of the IgG type can further be

divided into 4 subclasses: IgG1, IgG2, IgG3, and IgG4 (Araújo *et al*., 2003; Fiocruz, 2022). IgG4, under normal conditions, accounts for less than 5% of total IgG, being the least frequent (Suarez; Abril; Puerta, 2017).

IgG4-Related Disease (IgG4-RD) is a plasma cell lymphoproliferative condition, associated with increased levels of IgG4 and infiltration of IgG4-positive cells in affected structures. The progression of the inflammatory process generally leads to the development of storiform fibrosis, formed by spindle cells (Suarez; Abril; Puerta, 2017; Ito *et al*., 2019; Kawanami *et al*., 2021). The infiltration observed is characterized by the formation of germinal centers that increase the production of IgG4, consequently elevating its serum levels disproportionately to other IgG classes (Perugino *et al*., 2018; Ito *et al*., 2019).

Since 1892, there has been knowledge of patients with disorders compatible with the pathological findings of IgG4-RD. However, this concept was proposed and accepted only in the early second decade of the 21st century in Boston, and it is still in effect today (Suarez; Abril; Puerta, 2017).

Because it is a condition discovered relatively recently, there are still not enough studies to estimate its real incidence and prevalence. Most of what is known about the disease's epidemiology comes from the evaluation of case series, which suggest a higher frequency of involvement in men, mainly encompassing middle-aged and elderly individuals. There is no consensus on predilection in certain ethnicities, although the first reports of autoimmune pancreatitis were documented in Asians (Suarez; Abril; Puerta, 2017; Obiorah; Velasquez; Özdemirli, 2018; Wallace *et al*., 2019b).

The mechanisms involved in the pathophysiology of IgG4-RD are not fully understood. It is proposed that an as yet unknown factor would act as a trigger for the development of an adaptive immune response, leading to plasma cell infiltration in the affected organ. The protein galectin-3 has been studied in this context as it is believed to act as an antigenic target. Some autoantibodies associated with pathogenesis include: anti-pancreatic trypsin inhibitor, lactotransferrin, and carbonic anhydrase antibodies

(Suarez; Abril; Puerta, 2017; Perugino *et al*., 2019; Tsuboi *et al*., 2020; Kawanami *et al.*, 2021).

CD4+ T cells, in some models, are also implicated in the disease's pathogenesis by producing mediators that stimulate fibrosis development (Suarez; Abril; Puerta, 2017; Perugino *et al.*, 2019; Ito *et al*., 2019). Results from a study conducted by Ito *et al.* (2019) showed increased levels of regulatory follicular T cells (Tfr) in IgG4-RD patients compared to healthy individuals, as well as positively associating this increase with serum IgG4 levels and the number of organs involved.

There are still significant difficulties in diagnosing IgG4-RD, partly due to the various patterns of involvement that can be observed (Wallace *et al.*, 2019a). This study aims to highlight the main clinical manifestations that comprise the spectrum of IgG4-RD.

2. METHODS

This is a descriptive and qualitative integrative literature review, conducted on the databases Embase, PubMed, Science Direct, and Scientific Electronic Library Online (SCIELO), and Web of Science.

Four descriptors were used for literature search, obtained from MeSH (Medical Subject Headings) and DeCS (*Descritores em Ciências da Saúde*) platforms. In the former, "Immunoglobulin G4-Related Disease" and "Immunoglobulin G" were selected, while in the latter, "*Doença Relacionada a Imunoglobulina G4*" and "*Imunoglobulina G*" were chosen. The search in the listed databases was performed by combining or using these descriptors individually.

Article inclusion for this review was based on the following criteria: production within the last 6 years and focus on IgG4-Related Disease. Articles in languages other than Portuguese, English, or Spanish were excluded.

The selection of articles for this review occurred in two stages. Firstly, a search and subsequent reading of titles and abstracts of scientific productions were conducted,

selecting those that met the inclusion criteria. Subsequently, a full-text reading was performed to select the articles to be included in this review.

In PubMed, the descriptors "Immunoglobulin G4-Related Disease" and "Immunoglobulin G" yielded 239 results. After applying the inclusion and exclusion criteria, 42 productions were selected for detailed review, of which 29 were included in this review. In Science Direct, the descriptors "Immunoglobulin G4-Related Disease" and "Immunoglobulin G" yielded 9 results. Of these, 4 were selected for detailed reading, and all were included in the review. A search on Scielo with the descriptors "*Doença Relacionada a Imunoglobulina G4*" and "*Imunoglobulina G*" generated 1 result, which was selected for detailed reading but not included in this review. In Web of Science, the descriptors "Immunoglobulin G4-Related Disease" and "Immunoglobulin G" yielded 1 result, which was selected for detailed reading and included in the study. Finally, a search on the Embase platform with the descriptors "Immunoglobulin G4-Related Disease" and "Immunoglobulin G" generated 820 results, of which 7 were selected for detailed reading and 4 were included in the final analysis.

The analysis of the included studies was conducted by tabulating the following data from each article in a Microsoft Excel spreadsheet: author(s), affected systems, and manifestations. Finally, a synthesis of the obtained data was conducted descriptively and qualitatively.

3. RESULTS AND DISCUSSION

After applying the method, 38 articles were included in this study. In TABLE 1, the relationship between the types of involvement in specific organ systems can be visualized.

TABLE 1 - Main organs and systems affected within the spectrum of IgG4-RD and their respective clinical manifestations

Location	Manifestations	Reference
Kidneys	Tubulointerstitial nephritis in IgG4-RD	Al-Mujaini *et al*., 2018; Bhattad, Joseph, & Peterson, 2020; Gou *et al*.,

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		2018; Zheng, Teng, & Li, 2017
Nervous System	Hypertrophic meningitis due to IgG4-RD Spinal pachymeningitis due to IgG4-RD Hypertrophic pachymeningitis with polycystic subdural hygroma and hematoma in IgG4-RD IgG4-RD related hypophysitis	Alrashdi, 2020; Al-Mujaini *et al*., 2018; Bong *et al*., 2021; Boban, Ardal, & Thurnher, 2018; Gersey *et al*., 2021; Ota *et al*., 2020; Levraut *et al*., 2019.
Lungs	Pleuritis due to IgG4-RD Pulmonary IgG4-RD Pulmonary IgG4-RD with tracheobronchial nodules Pleural effusion caused by IgG4-RD	Al-Mujaini *et al.*, 2018; Kang *et al.*, 2020; Lv *et al*., 2018; Makimoto *et al*., 2019; Shimada *et al*., 2021; Wand *et al*., 2020; Wang *et al*., 2019.
Orbital orbit	Ocular lacrimal sac IgG4-RD Ocular IgG4-RD IgG4-RD associated with thyroid eye disease	Aryasit *et al*., 2021; Au *et al.*, 2020; Ye *et al*., 2020.
Liver	Hepatic atrophy due to IgG4-RD Autoimmune hepatitis due to IgG4-RD Sclerosing cholangitis due to IgG4-RD	Al-Mujaini *et al*., 2018; Chang *et al*., 2020; Fujita & Hatta, 2020; Goodchild, Pereira, & Webster, 2018; Matsumoto *et al*., 2019; Minaga *et al.*, 2019.
Pancreas	Autoimmune pancreatitis due to IgG4-RD	Al-Mujaini *et al.*, 2018; Matsumoto *et al*., 2019.
Stomach	Gastroesophageal IgG4-RD Gastric IgG4-RD Lymphoplasmacytic gastritis in IgG4-RD	Al-Mujaini *et al*., 2018; Khan *et al*., 2020; Seo *et al*., 2018; Skorus, Kenig, & Mastalerz, 2018.
Sistema vascular	Abdominal aortic aneurysm Aortitis Periaortitis Arteritis	Al-Mujaini *et al*., 2018; Peng *et al*., 2020; Prucha *et al.*, 2019.
Ovary	Ovarian IgG4-RDAk	Akyol *et al.*, 2020; Alorjani et al., 2020.
Testicle	IgG4-related testicular disease	Shams *et al.*, 2021.
Prostate	IgG4-related prostatitis	Al-Mujaini *et al.*, 2018.
Oral cavity	IgG4-RD involving the mandible	Tong, Ng, & Lo, 2017.
Head and neck	Eosinophilic angiocentric fibrosis	Ahn and Flanagan, 2018.

Skeletal muscle	IgG4-RD in biceps	Özdel *et al.*, 2020.
Abdomen	Abdominal mass Retroperitoneal fibrosis Sclerosing mesenteritis	Al-Mujaini *et al.*, 2018; Olmos *et al.*, 2021.
Skin	Cutaneous IgG4-RD Cutaneous pseudolymphoma in IgG4-RD	Al-Mujaini *et al.*, 2018; Ishimoto *et al.*, 2021.
Chest	Sclerosing mediastinitis in IgG4-RD Sclerosing mastitis due to IgG4-RD IgG4-RD inflammatory pseudotumors of the breast IgG4-related constrictive pericarditis	Al-Mujaini *et al.*, 2018.
Thyroid	IgG4-related thyroid disease and Fibrous Hashimoto's thyroiditis	Al-Mujaini *et al.*, 2018.

Source: Prepared by the authors (2023).

3.1 CLINICAL ASPECTS

IgG4-RD has a variable clinical presentation, and can affect a specific organ or several, synchronously or metachronously. The evolution is usually not acute, therefore symptoms such as fever, prostration, malaise, night sweats and even weight loss are uncommon (Al-Mujaini *et al.*, 2018; Obiorah; Velasquez; Özdemirli, 2018).

Clinically, allergy-related symptoms, lymphadenopathy and tumors occur in a considerable proportion of patients, who may have elevated IgE levels and peripheral blood eosinophilia (Al-Mujaini *et al.*, 2018; Obiorah; Velasquez; Özdemirli, 2018). Several of the clinical manifestations presented by patients with IgG4-RD are associated with the compressive effect of the tumor mass on adjacent structures, as well as on the affected organ itself (Obiorah; Velasquez; Özdemirli, 2018).

3.2 MAIN ORGANS AFFECTED

Overall, the most frequent involvements are pancreatic, orbital, salivary glands, and lacrimal glands (Al-Mujaini *et al.*, 2018). However, involvements in other sites, as

mentioned in TABLE 1, may be discovered, considering that IgG4-RD can occur virtually in any organ and that conditions previously considered as part of other diseases are now being classified within the IgG4-RD spectrum (Al-Mujaini *et al*., 2018; Obiorah; Velasquez; Özdemirli, 2018).

IgG4-RD was first reported in pancreatic involvements, in type 1 Autoimmune Pancreatitis (AIP), where histopathological evidence indicates lymphoplasmacytic sclerosing pancreatitis. A characteristic of IgG4-related AIP is the involvement of other structures such as kidneys, bile ducts, peritoneal fibrosis, lymph nodes, and orbital orbit. Involvement of the liver by IgG4-RD and the biliary duct system, in many cases, is associated with type 1 AIP (Obiorah; Velasquez; Özdemirli, 2018; Cargill *et al*., 2019).

The nervous system has a higher occurrence of cases in specific structures. When it occurs in the meninges, the picture is one of hypertrophic pachymeningitis, which can cause symptoms such as headache, seizures, or symptoms related to specific cranial nerve deficits, such as vision, motor, sensory deficits, among others. In cases where there is IgG4-RD in the pituitary gland, the symptoms depend on some characteristics of the mass such as its location and size, but generally, pituitary hormonal deficiencies occur (Obiorah; Velasquez; Özdemirli, 2018).

Regarding the involvement of lacrimal and salivary glands, the old disease of Mikulicz has been updated in nomenclature, so that when the site is the lacrimal gland, it is called IgG4-related dacryoadenitis, while in the case of inflammation of the salivary glands, the nomenclature has become IgG4-related sialadenitis. In terms of clinical presentation, there is usually the coexistence of type I AIP, interstitial nephritis, and negative antibodies such as anti-RO, anti-LA, antinuclear, and rheumatoid factor (Obiorah; Velasquez; Özdemirli, 2018).

Still, in cranial topography, even in rare described cases, otological, nasal, and throat involvements have been reported. The manifestation of nasal IgG4-RD can present as an invasive mass with destructive characteristics, including in nearby bony structures,

or it can present with a plasmacytic infiltrative pattern (Obiorah; Velasquez; Özdemirli, 2018).

In the orbital involvement of IgG4-RD, the manifestation is usually a disease in both orbits, painless, with symptoms associated with the presence of the mass in the region. It can involve structures such as lacrimal glands and ducts, sclera, extraocular muscles, local soft tissues, and nervous structures such as the trigeminal nerve (Obiorah; Velasquez; Özdemirli, 2018; Au *et al*., 2020).

When it comes to thyroid involvement in IgG4-RD, it is currently classified as Riedel's thyroiditis and fibrosing Hashimoto thyroiditis. Riedel's thyroiditis consists of chronic fibrosclerotic infiltrative disease, leaving the thyroid with a hardened appearance, while in fibrosing Hashimoto thyroiditis, it is characterized by layers of fibrosis and IgG4-positive plasma cell infiltrations (Obiorah; Velasquez; Özdemirli, 2018; Wu; Sun, 2019).

In the kidneys, in the context of IgG4-RD, there are two more common findings which are tubulointerstitial nephritis and membranous glomerulonephritis, clinically manifesting due to kidney dysfunction. In IgG4-related renal disease, tubular destruction and atrophy occur. The histological pattern of storiform fibrosis with good margin delimitation assists in differentiating between IgG4-RD and other primary forms of renal involvement (Zheng; Teng; Li, 2017; Obiorah; Velasquez; Özdemirli, 2018).

In the lungs, IgG4-RD manifests with nonspecific symptoms, and the patient presents with chest pain, dyspnea, and cough. IgG4-RD can present as interstitial disease or as a pseudotumor, which can be verified on imaging exams (Obiorah; Velasquez; Özdemirli, 2018).

Involvements of IgG4-RD in the Gastrointestinal Tract (GIT) present with infiltrative fibrosis and thickening of the GIT wall, as well as pseudotumors. Esophagitis and gastritis in IgG4-RD are mentioned in the literature with higher occurrences, although in the case of the esophagus, it is considered rare. The presence of neoplasia should be ruled out (Obiorah; Velasquez; Özdemirli, 2018).

IgG4-RD can also affect retroperitoneal structures, in most cases with characteristics of chronic and infiltrative inflammation. The symptoms are associated with the affected anatomical structure, as well as its expansion to adjacent structures, reaching the kidneys and inferior vena cava by compression. Periaortitis and periarteritis in IgG4-RD occur more commonly in the abdominal aorta, iliac, renal, and mesenteric arteries, which can evolve into a common complication in these cases, which is inflammatory aneurysm (Al-Mujaini *et al*., 2017; Obiorah; Velasquez; Özdemirli, 2018).

In the case of lymphadenopathy in IgG4-RD, it can occur in a specific topography or in a generalized form, being painless and of variable size up to 5 centimeters. IgG4-related lymphadenopathy has differential diagnoses such as lymphoma, infections, neoplasms, among others (Al-Mujaini *et al.*, 2018; Obiorah; Velasquez; Özdemirli, 2018).

Other involvements listed in TABLE 1, such as IgG4-RD in gonads, prostate, skin, oral cavity, and skeletal muscle, have had few studies and reported cases in the researched literature. Regarding skeletal muscle involvement, a Turkish publication by Özdel *et al.* (2020) emphasized that the case reported by them is the first in pediatric patients. In another Turkish study, Akyol *et al.* (2020) reported a case of bilateral ovarian involvement, with peritoneal involvement in a 58-year-old patient. Tong, Ng, and Lo (2017) reported a case of mandibular involvement in a 46-year-old woman in Hong Kong.

4. CONCLUSION

The vast range of manifestations of IgG4-RD is noted, varying in associated clinical impact, but which can characterize complicated conditions due to the possibility of affecting vital organs of the human body, including structures of the CNS, liver, and kidneys. In addition, the broad spectrum of conditions reported in the literature may suggest that virtually all organ systems are susceptible, although the evaluation of the literature has shown the greatest involvement of glandular tissues, especially the pancreas, which was indeed the first organ implicated in the spectrum of IgG4-RD manifestations.

Therefore, it becomes necessary to include the differential diagnosis of IgG4-RD in the evaluation of every patient with diseases whose proliferation at the primary site causes compression of adjacent structures, as well as in very nonspecific conditions where more common hypotheses have been ruled out. Further studies are needed for a better characterization of IgG4-RD, as manifestations that were once considered other diseases are now found within the spectrum of IgG4-RD.

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