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IgG4 Related Lung Disorder -A Review

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Abstract

IgG4 disorder is an autoimmune disorder. Its manifestation in the lung causes fibroinflammatory disorder. It is one of the chronic inflammatory disorders. IgG4 is the subclass of IgG. This review is analysed based on the IgG4 related disorder. Nearly 50 articles were reviewed and this study was conducted for a period of nearly 15 years.The IgG4 related disorder is a very rare disorder in the world. Moreover, It is an autoimmune disorder like Systemic lupus erythematosus. It is related to systemic disorder and chronic inflammatory disorder IgG4 varies high degree of fibrosis and it is prompted by the response of steroid therapy.It is the most common form of immunoglobulin. Ig G also known as secretory immunoglobulin.Ig G4 is a subclass of IgG comprising only 4% in gamma immunoglobulins . IgG4 does not bind to polysaccharides. Increased levels of IgG4 in serum usually found in patients suffering sclerosing pancreatitis, cholangitis and interstitial pneumonia caused by the infiltration of IgG4 positive plasma cells. IgG4 has a molecular weight of 159. IgG4 related disorder recognised as one of the rare autoimmune disorders which can affect multiple organs and cause organ failure sometimes. It involves the complement system and interacts with the antibody. Generally IgG4 related disorder is recognised as one of the most rare autoimmune disorders which can affect multiple organ failure sometimes. It involves complement system and interact with antibody. Generally, IgG4 related disorder most commonly present in in beekeper, animal laboratory workers and individuals who have undergone allergen immunotherapy possess high serum level of IgG4.it is one of the acquired Type II hypersensitivity disorder. This review mainly aims to know the reason behind the clinical lung disorder.

Keywords*: IgG4, Complement system, autoimmune disorder, treatment, clinical findings*

Introduction

Ig G4 is a subclass of IgG comprising only 4% in gamma immunoglobulins . IgG4 does not bind to polysaccharides. Increased levels of IgG4 in serum usually found in patients suffering sclerosing pancreatitis, cholangitis and interstitial pneumonia caused by the infiltration of IgG4 positive plasma cells. IgG4 has a molecular weight of 159. 12 amino acids are found in the hinge region, two inter H chain disulfide bonds are found. Normal serum level of IgG4 is 0.56 g/l. IgG4 related disorder is a novel recognised fibroinflammatory disorder and it is usually manifest as generalised swelling in various organs with pathologic findings showing the IgG4 rich plasma cell infiltration, chronic inflammation and fibrosis. It may involve any organ showing the elevated serum IgG4 concentration[1]. The initial differential diagnosis for IgG4 related disorder includes panbronchiolitis, an inflammation found in bronchioles which causes severe cough,large amount of sputum and exertional breathlessness,sarcoidosis and the hypersensitive pneumonitis.In chest computed tomography, it reveals the bilateral diffuse centrilobular

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nodules, tee in bud pattern, bronchial wall thickening and multifocal ground glass opacities. It shows some mediastinal lymph node enlargement and also shows multiple mosaic attenuation.[2]. It may involve multiple organs including lungs, mediastinum , liver and pancreas. It is characterized by tumefactive lesions with lymphoplasmacytic infiltrates with abundant IgG4 positive plasma cells, storiform fibrosis and usually elevated serum IgG4 concentration[3]. This disease is also related to numerous conditions like autoimmune pancreatitis, Riedel thyroiditis, tubulointerstitial nephritis[4]. The clinical treatment for IgG4 can be found by reviewing the articles.There are certain drugs administered in this disorder like Glucocorticoid, azathioprine, 6 mercaptopurine, cyclophosphamide, rituximab are given. In this article, morphological views can be found.Glucocorticoid is the first line drug used in treatment of IgG4 related disorders we can find remission induction in all patient is active, conditions which mimics IgG4 related disease are inflammatory bowel disease, Rhinosinusitis, sjogren syndrome, sarcoidosis, xanthogranuloma,splenic sclerosis[5]. The Etiological factor of IgG4 Related disorder could be congenital or acquired [6] the lymphocytic infiltration is seen in respiratory disorder.[7]Usually the stye is seen in this disorder observed in the monkey[8]. The stye is an infection of sebaceous gland [9] This study mainly focuses to know the reason behind the every clinical symptoms produced in IgG4 related lung disorder.The article can be reviewed with the help with the help of search engine. Nearly 36 articles are reviewed with the help of search engines. The articles were collected based on their pathogenesis , clinical manifestation, diagnosis, treatment of IgG4 related disorder. The period of study from 2005 -2020. The article which is not related with this review other than IgG4 related disorder, IgG4 related cardiovascular system, IgG4 related kidney are not considered.

LUNG DISORDERS RELATED TO IgG4

IgG4 Related to Interstitial Lung Disorder

IgG4 disorder is related with IgG4 positive plasma cell suggestive of grade 1 lymphomatoid granulomatosis. presence of IgG4 positive plasma cell with lack of atypical cell favours IgG4 related disorder[10]. IgG4 related interstitial lung disease have shown without any systemic manifestation have been reported.The pathological findings are examined reveals that the thickening of bronchovascular bundle and alveolar septa by infiltration of plasma cell , lymphocyte and few eosinophils.[11]There is an increased attenuation to IgG4 related lung disorder is seen and it is characterized by elevated serum IgG4 level and IgG4 positive plasma cell infiltration into multiple target organs includes lung.[12]IgG4 related disease is characterized by by high serum IgG4 concentration,sclerosing inflammation with numerous IgG4 positive plasma cell and steroid sensitivity irrespective of any organs[13] Immunostaining shows the infiltrations present in interstitium of CD3 positive T cell and CD 20 positive B cell as well as numerous CD38 positive, IgG4 positive plasma cells.[14] The X ray finding tells that there is ground glass appearance and honey comb associated with interstitial pneumonia[15] Respiratory disorder is the most common disorder in the world and its prevelence is seen among old aged patient[16]The count of white blood is decreased generally in the autoimmune disorder like IgG4 disorder, sjogren syndrome,multiple sclerosis,etc.[17]The Infiltration of IgG4 in the Alveolar septum is clearly visible in immunostaining. Interstitial pneumonia is strongly associated with autoimmune pancreatitis. There is an infiltration of IgG4 positive plasma cells were also observed.[18]

IgG4 Related Lung Disorder Diagnostic Feature:

Elevated IgG4 serum level is the key to confirm the IgG4 related disorder. It shows the presence of hypergammaglobulinemia, hypocomplementemia, tissue eosinophilia, and the lymphoplasmacytic infiltration.[19] The gold standard diagnosis of IgG4 Related disorder , identification of typical histopathologic feature (i.e., rich lymphoplasmacytic infiltration, storiform infiltrate, obliterative phlebitis) in context of significant IgG4 positive plasma infiltrate.[1]. Elevations in serum IgG4 concentration is considered as one of the most important diagnostic features in IgG4 related disorder. Most of the research articles shows that the IgG4 Related Disorder shows the various organ manifestation particularly in organs like pancreas, kidney, biliary tree appearance, salivary gland.[20] The cardinal feature of IgG4 related disorder or multiple organ swelling that are often considered as increased concern for malignancy[21]there is the relative predominance of lymphoplasmacytic

and sclerotic components like pseudolymphomatous, mixed and sclerosing.[22] The histopathologic diagnosis of the IgG4 related lung disorder is always the best in identification of IgG4 related lung disorder. It is often related to the abundent infiltration of IgG4 positive plasma cells. The patients with this disorder were shown to have immunocompromised problems[23]. So the histopathological picture of disorder is a very important aspect.[24] Usually for the histopathological study, the microscopic slide paraffin should be added for clear visibility.[25]

Pathogenesis of IgG4 Related Disorder:

IgG4 related lung has an analogue to sarcoidosis, another systemic disease in which the diverse organs manifestation linked by the unique histological appearance.Disparate disorder such as Mikulicz syndrome,kutter tumour, multifocal fibrosclerosis and eosinophilic angiocentric fibrosis [22]. The two main features that links disparate manifestation of IgG4 related disorder are characteristic of histological appearance and elevated IgG4 positive plasma cell within the tissues.[1] The serum IgG4 concentration upto 40% of patients have shown biopsy proven IgG4 related disorder.[26] There are some studies have shown the correlation between the Helicobacter pylori and constituent of pancreatic epithelial cell suggest gastric Helicobacter pylori infections triggers the autoimmune pancreatitis in genetically predisposed individuals through antigen antibody cross reaction. It involves activation of many complementary systems.[27] [28]The significant role of Th2 cytokines with the contribution of innate immunity factors such as toll like receptors, macrophages and basophils.The alveolar macrophages are activated by interleukins which causes inflammation are overexpressed by the B-cell activating factor and contributes to the chronic inflammation which causes the development of fibrosis.[29] Wheezing is commonly seen in patients with respiratory problems and old aged patients. The only way to alleviate wheezing is breathing exercise.[30]

Treatment of IgG4 Disorder with Drugs

IgG4 related lung disorders treated with rituximab have shown a prompt decrease in IgG4 serum level. The level of liver enzymes gradually decreased and continued to decrease further after 6 months administration of rituximab.[31] . Although rituximab shows the adverse effect like B cell depletion it is effectively used in treatment of IgG4 related disorder.[32] Rituximab is a chimeric monoclonal antibody which is directed against the B lymphocytes which has a specific antigen CD 20. CD 20 is first expressed in bone marrow.[33]Glucocorticoids and B cell depletion strategies appear to be effective[34] Corticosteroid treatment for this disease follow-up for two months have shown the complete resolution of the disease.[35] Dupilumab is a monoclonal antibody directed against the interleukins and also inhibits the signalling of cytokines. It is potentially used in treatment of allergies and atopic diseases.Subcutaneous administration of dupilumab have shown poor control on atopic manifestation. It is a steroid sparing drug.[36]Dupilumab is a drug which serves as an effective in treatment of the IgG4 related disorder and it is also considered as safe drug though has adverse effects.[37]Usually the stem cells also been used as one of the treatment procedure for treating the IgG4 related disorder[38] The radiotherapy is also in treatment but it can impose various damage to the cells[39]the red blood cell count is relatively decreased[40].In order to avoid that fruit consumption should be there.[41]

Clinical Features of IgG4 Related Disorder

IgG4 Related disorder involves multiple organs which causes faIlure. The affected organs show the orbital pseudotumor [A renal mass Decembers renal cell carcinoma] and nodular lesion in lungs. Lymphadenopathy is the common clinical feature in IgG4 or related disorder.Asthma and allergies present nearly in 40% of the patients. There is a presence of solid nodular , thickening of bronchovascular and interlobular septa, alveolar interstitial resembling the honeycomb , bronchiectasis and diffuse ground glass opacity.[42]Physical examination of IgG4 related disorder patients has shown reduced breathing sound at the bottom of lung and blood gas analysis reveals moderate hypoxemia. Blood test revealed that there is mild anaemia, increased inflammatory marker (erythrocytes sediment rate, and C reactive protein) and increased plasma level IgG4 (230mg/dL).CT scan of lung reveals the partially organized left pleural effusion, small area of atelectasis in lingula and anterior basal segment of left lower lobe and increased volume of lymph node seen in paratracheal and subcarinal station. IgG4 related disorder affects any organ with exception of synovium which is

usually present in joints.Haematological findings have revealed lymphadenopathy, eosinophilia and polyclonal hypergammaglobulinemia.[43].

Lung manifestation of IgG4 related disorder revealed to be diverse. They include disease tracks along the bronchi and blood vessels. Images have revealed pulmonary nodules, ground glass opacities, pleural thickening or interstitial lung disease[44]. The clinical symptoms include cold, cough, haemoptysis, dyspnea, pleural effusion and chest pain are present. Many patients with IgG4 related disease have shown allergic features like atopy is seen, eczema, chronic sinusitis and asthma are seen in this disorder. It causes irreversible tissue damage to any organs.[45,46] Some patients have presented the infection of pneumonias, deep vein thrombosis, gastrointestinal bleeding during the treatment of steroid. It has been reported that one patient have died due to presence of IgG4 related disease with respiratory failure due to pneumonia for eight months after the glucocorticoid therapy.[4748] Histopathological features are lymphoplasmacellular infiltration with IgG4 positive plasma cell Storiform fibrosis and obliterative phlebitis. This leads to functional destruction. There is a presence of a mixture of Th1 and Th2 cytokines immune response whereas the role of pathogenic IgG4 antibodies are still unclear. Occurrence of this disease in organs due to dysregulation of the immune system.[49]

Conclusion

To conclude, IgG4 is a rare autoimmune disorder manifested due to lymphoplasmacytic infiltration and elevated serum IgG4 positive cells. It can also manifest multiple organ failure. Glucocorticoids being the first line drug for IgG4 related disorder, other drugs like rituximab, dupilumab and other steroidal therapies were also recommended to treat the IgG4 related lung disorders. This review had thus provided an overview of the IgG4 associated lung disorders and its associated therapeutic measures with its limitations and challenges.

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