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Liver cirrhosis with high IgG4 in a patient with, diabetes mellitus, ulcerative colitis with papillary thyroid cancer, is it all related ? which one to blame& is it time to raise awareness about IGG4 and hepatobiliary diseases

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ABSTRACT

Back ground: There is possible etiological relation between high IgG4 in a patient with liver cirrhosis, ulcerative colitis, diabetes mellitus , prostatitis ,venous thrombosis and thyroid cancers and the use of immunosuppressive & biologic agents.

Method: a study of patient with multiple organ involvement with persistently elevated IgG4. A 56 years old male with persistently elevated IgG4 over 2.5 times normal level, diabetic on insulin, ulcerative colitis on azathioprin & adalimumab developed deep skin pigmentation and liver enzymes elevation with portal hypertension and liver cirrhosis, azathioprine & adalimumab were stopped and golimumab started, after 3 infusions of golimumab papillary thyroid cancer developed .Total thyroidectomy followed by radio iodine after which severe sialoadenitis developed which responded to steroids. His ulcerative colitis was treated with vedolizumab with good response. liver cirrhosis progressed with bleeding varices and portal vein thrombosis with factor Leiden V mutation. **Results and conclusions:** High IgG4 can be related to many organs including pancreas,liver,thyroid ,small and large bowel,parotid glands ,in this patients all these were affected resulting in colitis,diabetes,liver cirrhosis and thyroid cancer and sialoadenitis. Awareness is needed on the associations with high IgG4. **Conclusion:** A patient with elevated IgG4 , liver cirrhosis , diabetes mellitus, ulcerative colitis developed skin pigmentation, and papillary thyroid cancer associated with persistently elevated IgG4.

Keywords: IgG4 related, liver cirrhosis ,diseases, diabetes mellitus, ,thyroid cancer

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Background

IgG4-related disease (IgG4 RD) is a fascinating clinical entity including a wide variety of diseases, formerly diagnosed as Mikulicz's disease, autoimmune pancreatitis (AIP), interstitial nephritis, prostatitis and retroperitoneal fibrosis.

Characteristics common to all forms of IgG4-RD include elevated serum IgG4 concentration and tissue infiltration by IgG4-positive plasma cells, accompanied by tissue fibrosis and sclerosis.

As increased serum concentrations of IgG4 have been observed in several diseases with aberrant immunological condition unrelated to IgG4-RD, such as malignant tumors, autoimmune diseases especially rheumatoid arthritis and allergic diseases, increased IgG4 concentration is not a specific marker for IgG4-RD.

In contrast, recent large cohort studies from the UK, Taiwan and Japan showed that serum IgG4 concentration >135 mg/dL had overall sensitivities of 82.8%, 86% and 88%, respectively, in diagnosing IgG4-RD.

Since this complex multisystem disease represented a single pathogenetic disorder manifesting in a variety of target organs, the diagnosis of IgG4-RD is largely based on biopsy results showing enhanced infiltration by IgG4-positive plasma cells, storiform fibrosis,

obliterative phlebitis and moderate eosinophilia, all of which are frequently observed in the affected tissues of these patients.

A high number of IgG4-positive plasma cells in tissue is a hallmark of IgG4-RD, even when serum IgG4 concentrations are below the cut-off level.

IgG4-RD tends to be both under diagnosed and over diagnosed.

Under diagnosis is due to a lack of recognition of this disease, and over diagnosis results from the well intentioned enthusiasm of physicians and/or pathologists who recognize IgG4-RD and diagnose similar conditions as IgG4-RD.

A definite diagnosis of IgG4-RD by CD criteria requires all three diagnostic characteristics:

- Clinical evidence,
- High (>135 mg/dl) serum igg4 and
- Pathological certification (>10 igg4+ cells/hpf and igg4+/igg cell ratio >40%),

Some patients may not satisfy these specific serological and /or histopathological criteria because of the difficulty of obtaining biopsies, and therefore cannot be diagnosed with definite IgG4-RD.

Several Japanese medical societies, including those for gastroenterology, pancreas, biliary tract, rheumatology, ophthalmology and respiratory, have published organ specific criteria for IgG4-RD.



Figure 1 colonoscopy 2016 left sided ulcerative colitis



Figure 2 Gastroscopy 2016 early esophageal varices

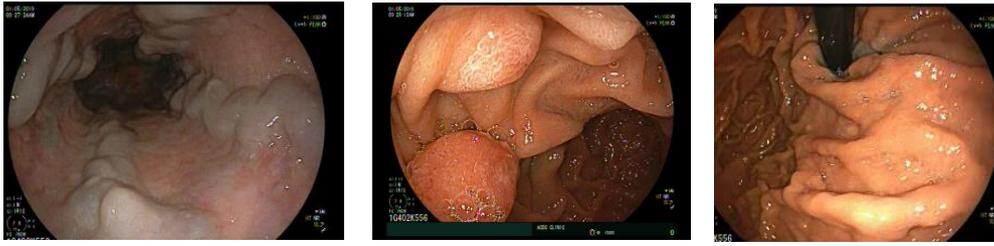


Figure 3 Gastroscopy 2019 extensive varices with duodenal inflammatory poly

Each criterion contains organ-specific clinical symptom and characteristic radiological findings of IgG4-RD, even with steroidal trial in some.

We reported our initial experience in the United Arab Emirate on high IGG4 associated with pachymeningitis, inflammatory bowel diseases, celiac disease, thyroiditis, retroperitoneal fibrosis, auto immune pancreatitis & sclerosing cholangitis. (Letter to the Editor AMJ 2019 12(3))

Case study and lessons learned

Male 55 BMI 25, with strong family history of diabetes mellitus & myocardial infarctions in brothers and father.

His diabetes mellitus started 1997 treated with oral hypoglycemics, insulin started 2005, developed ulcerative colitis 2015 treated with mesalazine 3.2 g, azathioprine 200mgm and courses of budesonide 9 mg.

Because of the colitis (Fig 1) frequent relapses, adalimumab was started Jan 2016.

July 2016 developed recurrent deep vein thrombosis lower limbs then portal vein thrombosis and discovered to have factor V Leiden mutation, treated with oral anti-coagulants.

Hematuria developed, ultrasound showed small bilateral kidney stones with large prostate.

2018 because of darkening of the skin and elevation of the liver enzymes, azathioprine was stopped and continued on adalimumab.

Because of relapses with adalimumab ,golimumab infusions was started July 2018 only 3 doses given but the patient developed

thyroid swelling proved to be follicular thyroid cancer.

Golimumab was stopped and total thyroidectomy followed by radio iodine therapy after which developed severe sialoadenitis of the mandibular glands that resolve on steroids.

His IgG4 was repeatedly elevated high over 250- 300 (normal 84)

2018 September, Vedozilumab started for his ulcerative colitis relapse.

March 2019 developed severe anemia Hb dropped to 7 grams- urgent gastroscopy (Figures 2,3) showed grade 4 esophageal varices with duodenal inflammatory polyp, varices band ligated.

Currently stable with hepatosplenomegaly, esophageal varices, portal vein thrombosis on oral anti-coagulants, insulin and vedozilumab, last IgG4 was 214 (N 86)

Summary

A patient with persistently elevated IgG4, diabetes mellitus, ulcerative colitis prostatitis, treated with azathioprin, adalimumab, golimumab & lately vedozilumab, developed liver cirrhosis, & papillary thyroid cancer which may all be related to IgG4.

key points are:

1. The high IgG4 is possibly related diabetes ,ulcerative colitis, liver damage ,thyroid cancer ,more studies needed
2. Diabetes and rising hepatobiliary cancers need to study the relation to IgG4
3. The safety of biologic agents and relation to cancer and safety after cancer treatment ? which biologic is more safe, is the new oral

biologics like tofacitinib safer in ulcerative colitis ?

4. The reaction to radio iodine with sialo adenitis may be related to high IgG4.
5. In complex diseases like this with diabetes, liver cirrhosis with portal hypertension and ulcerative colitis, if he need liver transplant in the future, would it be a cluster transplant, liver, pancreas with colectomy? would igg4 affect the scenario?

Conclusions

IGG4 is increasingly recognized entity and can be associated with a variety of gastrointestinal and hepatobiliary manifestations including auto immune pancreatitis, sclerosing cholangitis, inflammatory bowel diseases more with ulcerative colitis than Crohns disease, celiac disease in addition to involvement of salivary and thyroid glands.

In our patient he has persistently elevated IgG4 with multiple pathologies including: ulcerative colitis,thyroid cancer,diabetes mellitus,liver cirrhosis and recurrent venous thrombosis.

The relation to the high IgG4 could be causative or an associated phenomena and need further studies to clarify the link.

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