Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders

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ABSTRACT

Background IgG4-related systemic fibrosclerosis is a recently defined disorder characterised by a diffuse or tumefactive inflammatory reaction rich in IgG4-positive plasma cells associated with sclerosis and obliterative phlebitis. Although characteristic histopathological features are essential for the diagnosis of these disorders, to date there exists no consensus regarding the cut-off values used to define a 'significant IgG4-positive plasma cell count,' and data regarding the distribution of IgG4-positive plasma cells under common (non-specific) inflammatory conditions are lacking.

Methods The authors analysed 121 randomly selected histopathological specimens containing prominent lymphoplasmacytic infiltrates (11 obstructive sialadenitis, 27 inflammatory lesions of the oral cavity, 24 inflammatory gastrointestinal lesions, 15 rheumatoid synovitis, 15 non-specific synovitis, eight non-specific dermatitis and 21 primary carcinomas with a peritumoral inflammatory response). For comparison, seven cases of sclerosing sialadenitis (Küttner tumour) were examined.

Results High counts of IgG4 plasma cells were found in sclerosing sialadenitis (mean 40/high-power field (hpf)), contrasting sharply with sialadenitis caused by sialolithiasis (mean 3/hpf). Greatly varied but generally high counts of IgG4-positive plasma cells were also seen in several of the other lesions, particularly in rheumatoid synovitis (mean 55/hpf), oral cavity lesions (mean 79/hpf) and carcinoma-associated inflammatory response (mean 24/hpf). The mean IgG4/IgG ratios for all lesions varied between 0 and 0.4.

Conclusions The results demonstrate the ubiquitous occurrence of variably high numbers of IgG4-positive plasma cells under diverse non-specific inflammatory conditions, indicating that high IgG4-positive plasma cell counts and high IgG4/IgG ratios per se do not reliably distinguish IgG4-associated systemic disease from non-specific conditions, and that the IgG4 counts must be cautiously interpreted in the context of appropriate clinical and histopathological features.

INTRODUCTION

IgG4-associated sclerosing disease (ISD) has emerged recently as a unifying concept for several previously described inflammatory organ-specific conditions characterised by an elevated serum level of IgG4 and the occurrence of sclerosing lymphoplasmacytic inflammatory reaction rich in IgG4-positive plasma cells in one or more organs.^{1–4} Autoimmune pancreatitis (AIP) represents the

prototype of these disorders and has been the subject of extensive studies.^{5–8} Recent publications have documented similar lesions in almost all body organ systems, including in particular sclerosing cholangitis,⁹ sclerosing sialadenitis/Küttner tumour,^{10–11} chronic sclerosing dacryocystitis,¹² idiopathic retroperitoneal fibrosis,¹³ sclerosing angiomatoid nodular transformation of the spleen¹⁴ as well as IgG4-related renal,¹⁵ lymphadenopathic,¹⁶ hypophyseal,¹⁷ mediastinal,¹⁸ pleuropulmonary¹⁹ and soft-tissue²⁰ diseases. The diagnosis of any of these conditions is based on a set of both clinical and histopathological features. Dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells accompanied by a prominent (typically storiform) sclerosis and obliterative phlebitis are considered the histopathological hallmarks of ISD.

As these fibroinflammatory conditions frequently present as tumefactive lesions, concern about malignancy may prompt biopsy of the lesion. Thus, pathologists are increasingly being confronted with this differential diagnostic challenge. Several working groups have attempted to define a set of diagnostic criteria based on clinical and histopathological characteristics which allows a precise and reliable diagnosis of AIP and other ISD. However, the reliability of histopathological evaluation in the diagnosis of ISD has been challenged by the fact that variable recommendations exist by different working groups, in particular regarding the most appropriate threshold to define a 'significant IgG4-positive plasma cell count.' Thus, variable cut-off values of >10 ,⁵ >20 ,^{21–22} >20 ,^{23–24} and >50 ,²⁵ IgG4-positive plasma cells/high-power field (hpf) have been used to define AIP in different publications. Other groups have suggested a four-tiered scoring system to assess the severity of IgG4-positive plasma cell infiltrates as severe (>30 /hpf), moderate (10–30/hpf), slight (5–10/hpf) and few (<5 /hpf).^{26–27} However, this scoring system does not take into account the density of plasma cell aggregates and thus does not help to distinguish between 'real' ISD and lesions that fall into the 'physiological' range of IgG4-positive plasma cell infiltration in ordinary non-specific inflammatory conditions. The use of IgG4/IgG ratios proved to be more valuable in identifying ISD than the absolute counts of IgG4 plasma cells. In their cross-sectional study of 115 cases of ISD in the most recent study, Zen *et al* used an IgG4/IgG ratio of 0.3 as a threshold for the diagnosis of ISD.²⁸ To our knowledge, the distribution and ranges of IgG4-positive plasma cells as

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a possible component in ordinary (non-specific) chronic inflammatory conditions from different organ systems have not been sufficiently studied yet. This was the aim of this study.

MATERIAL AND METHODS

Case material and selection criteria

We analysed 121 specimens from 121 patients (100 chronic plasma cell-rich inflammatory conditions and 21 carcinoma specimens with a prominent peri-/intratumoral inflammatory response) retrieved from the routine surgical pathology files at our institution. The inflammatory conditions included 11 cases of obstructive sialadenitis caused by sialolithiasis, 27 inflammatory lesions of the oral cavity (12 cases of plasma cell epulis, 11 cases of radicular cyst/apical granuloma, four cases of lichen ruber), 24 lesions of the lower gastrointestinal tract (nine cases of Crohn disease, nine cases of ulcerative colitis, six cases of sigmoid diverticulitis), 15 cases of clinically proven rheumatoid synovitis, 15 cases of non-specific synovitis (five cases of Perthes disease, 10 cases of degenerative joint disease), and eight cases of plasma cell-rich dermatitis (four cases of lichen sclerosus et atrophicus, two cases of anus praeter associated inflammatory reaction and one case each of posthitis and unguis incarnatus). In addition, 11 squamous cell carcinomas (four vulva and seven oral cavity) and 10 adenocarcinomas (four pancreas, two colon, two lung, two breast) with an antitumoral inflammatory response rich in plasma cells were included. Based on the available clinical records, none of the patients included had clinical signs of AIP or other condition related to ISD. Age was not a criterion in case selection, and a wide age range has been included as determined by specimen type. For comparison purposes, seven cases of IgG4 associated sclerosing sialadenitis (Küttner tumour) were stained. This study is covered by ethical votum of the medical faculty of the University of Erlangen-Nuremberg.

Immunohistochemistry

Tissue samples were routinely fixed in buffered formalin and embedded in paraffin. Immunohistochemistry was carried out on 4 µm sections using a polymer Kit purchased from Zytomed systems (Berlin, Germany) according to the manufacturer's instructions and the following antibodies: rabbit polyclonal

antibody against human IgG (1:2000, DAKO, Denmark, pretreatment with Pronase), mouse monoclonal antibody against human IgG4 (clone MCA2098G, 1:100, SeroTec, UK, pretreatment with citrate buffer) and mouse monoclonal antibody against human CD138 (clone Mi15, 1:500, DAKO, Denmark, pretreatment with citrate buffer).

H&E-stained sections and sections stained with CD138 were evaluated, and the area with the highest density of plasma cell infiltration was identified and marked. IgG-positive and IgG4-positive plasma cells were counted in five high-power fields (one hpf corresponded to an area of 0.238 mm²) within the previously marked areas with the highest plasma cell infiltration. The mean number of positive cells per hpf and the ratios of IgG4:IgG-positive plasma cells were calculated. Examination of tissue samples treated with IgG4 antibody revealed subsets of IgG4-positive and IgG4-negative plasma cells, thus demonstrating the specificity of the staining. Only cells with clear-cut strong cytoplasmic reactivity were considered positive.

Statistical analysis

The Student t test was used to assess the statistical significance between different groups. A p value of <0.05 was considered significant, and a p value of <0.01 was considered highly significant.

RESULTS (summarised in Table 1)

Chronic obstructive sialadenitis and sclerosing sialadenitis/Küttner tumour

Seven cases of autoimmune sclerosing sialadenitis (Küttner tumour) were examined for comparison purposes. The seven cases showed an average of 40 IgG4-positive plasma cells/hpf (range 4–104/hpf). The IgG4/IgG ratio varied from 0.23 to 0.73 (mean 0.59) (figure 1A–C). In contrast, the 11 cases of non-specific obstructive sialadenitis associated with sialolithiasis showed low counts of IgG4-positive plasma cells/hpf, the values ranging from 0 to 27/hpf (mean 3/hpf) with a mean IgG4/IgG ratio of 0.02 (range 0–0.15). Statistical analysis demonstrated a significant difference between absolute IgG4 plasma cell counts (p=0.023) and IgG4/IgG ratios (p=0.0018) regarding the groups of Küttner tumour and sialolithiasis-associated sialadenitis.

Table 1 Distribution of the IgG4 counts and the IgG4/IgG ratios in the study cohort (n=128 including the seven Küttner tumour cases)

Localisation	Diagnosis	n	Mean IgG4/hpf	Range IgG4/hpf	Mean IgG/hpf	IgG4/IgG mean ratio	Range IgG4/IgG ratio
Salivary glands	Sclerosing sialadenitis/Küttner tumour	7	40	4–104	74	0.59	0.23–1
	Sialadenitis caused by sialolithiasis	11	3	0–26.8	54.0	0.02	0–0.15
Oral cavity	All lesions	27	79	0–235	235	0.32	0–0.84
	Epulis plasmocellularis	12	69	27–102	232	0.32	0.18–0.77
	Radicular cysts	11	93	23.3–234	278	0.32	0.1–0.84
	Oral lichen ruber	4	67	0–217	126	0.35	0–0.84
	All lesions	24	11	0–40	187	0.06	0–0.2
Lower gastrointestinal tract	Crohn's disease	9	8	1–22	160	0.046	0.008–0.08
	Ulcerative colitis	9	8	0–18	210	0.04	0–0.06
	Diverticulitis	6	19	0–40	194	0.11	0–0.2
	All lesions	30	35	0–181	122	0.27	0–1
Synovitis	Rheumatoid arthritis	15	55	0–181	153	0.4	0–1
	Non-specific synovitis	15	15	0–79	92	0.15	0–0.44
	All lesions	21	24	0–88	117	0.22	0–0.51
Carcinomas	Adenocarcinomas	10	6	0–88	73	0.21	0–0.48
	Squamous cell carcinomas	11	34	1–81	156	0.23	0–0.51
	All lesions	8	26	1–120	85	0.21	0.04–0.67
Skin	All lesions	8	26	1–120	85	0.21	0.04–0.67

hpf, high-power field.

Figure 1 Representative images of H&E (left column), IgG4 (mid-column) and IgG (right column) from chronic inflammatory conditions (original magnification: 200 $\times$). (A–C) Sclerosing sialadenitis, Küttner tumour. (D–F) Rheumatoid synovitis. (G–I) Non-specific synovitis.

IgG4-positive plasma cells in rheumatoid synovitis and non-specific synovitis

In the 15 cases of clinically proven rheumatoid synovitis (figure 1D–F), the counts of IgG4-positive plasma cells ranged from 0 to 181/hpf (mean 55/hpf), and the IgG4/IgG ratio varied between 0 and 1.0 (mean 0.4). In contrast to this, the 15 cases of synovitis without a clinical diagnosis of rheumatoid arthritis showed a significantly lower level of IgG4-positive plasma cells (mean 15/hpf; range 0–79) (figure 1G–I). The IgG4/IgG ratio in the non-specific synovitis cases ranged between 0 and 0.44 (mean 0.15). Interestingly, three cases from the non-specific synovitis group displayed high IgG4-positive plasma cell counts (between 40 and 79 IgG4-positive plasma cells/hpf; IgG4/IgG ratio between 0.4 and 0.72). In one of these cases, the histological findings were suggestive of rheumatoid arthritis, but clinical data were inconclusive, and an infectious aetiology could not be definitely ruled out. Statistical analysis showed a significant difference between both the absolute IgG4 plasma cell counts ($p=0.014$) and the IgG4/IgG ratios ($p=0.027$) regarding the groups of rheumatoid synovitis and non-specific (non-rheumatoid) synovitis.

IgG4-positive plasma cells in chronic inflammatory lesions of the oral cavity

Taken together, the 27 inflammatory oral lesions showed a mean of 79 IgG4-positive plasma cells/hpf (range 0–235/hpf). The IgG4/IgG ratios ranged from 0 to 0.84 (mean 0.32). The mean

IgG4-positive plasma cell counts were 69 and 93/hpf for the plasma cell epulis and radicular cysts/apical granuloma cases respectively. The four cases of lichen ruber mucosae showed a mean of 67 IgG4-positive plasma cells/hpf. The respective mean IgG4/IgG ratios were 0.32 for plasma cell epulis and radicular cyst/apical granuloma and 0.35 for lichen ruber mucosae. The numerous IgG4-positive plasma cells were generally evenly distributed throughout the lesion in all the oral cavity lesions with occasional small dense aggregates (figure 2A–C).

IgG4 in chronic inflammatory conditions of the lower gastrointestinal tract

The nine cases of Crohn disease showed a mean of 8 IgG4-positive plasma cells/hpf (range 1–22/hpf). The IgG4/IgG ratio varied between 0 and 0.08 (mean 0.05). The nine cases of ulcerative colitis showed similar counts of IgG4-positive plasma cells (1–18/hpf; mean 8/hpf) with an IgG4/IgG ratio between 0 and 0.06 (mean 0.04). Furthermore, six cases of sigmoid colon diverticulitis were assessed. Here, the IgG4-positive plasma cell count varied between 0 and 40/hpf (mean 19/hpf), with an IgG4/IgG ratio between 0 and 0.2 (mean 0.11). Taken together, gastrointestinal tract lesions showed a mean of 11 IgG4-positive plasma cells per hpf (range 0–40/hpf), and the IgG4/IgG ratio ranged between 0 and 0.2 (mean 0.06). Statistical analysis showed a highly significant difference regarding the absolute IgG4 plasma cell numbers ($p<0.001$) and the IgG4/IgG ratio

Figure 2 Representative images of H&E (left column), IgG4 (mid-column) and IgG (right column) from chronic inflammatory conditions (original magnification: 200 $\times$). (A–C) Plasma cell epulis. (D–F) Unguis incarnatus. (G–I) Squamous cell carcinoma. (J–L) Adenocarcinoma.

($p < 0.001$) when comparing the lesions of the lower gastrointestinal tract with the oral cavity lesions.

IgG4 in non-specific dermal inflammatory infiltrates

This small subgroup of eight benign chronic inflammatory conditions of the skin showed between 1 and 120 IgG4-positive plasma cells/hpf (mean 26/hpf). The IgG4/IgG ratio varied between 0.04 and 0.67 (mean 0.42) (figure 2D–F). The four cases of lichen sclerosus et atrophicus showed only sparse infiltrates of IgG4-positive plasma cells (0–5/hpf, mean 2) with a ratio between 0.04 and 0.06 (mean 0.05). The highest density of IgG4-positive plasma cells was found in the case of unguis incarnatus (120/hpf; IgG4/IgG ratio 0.67).

IgG4-positive plasma in tumour-associated inflammatory response

For the group of carcinomas as a whole ($n=21$, 10 $\times$ adenocarcinoma, 11 $\times$ squamous cell carcinoma), the IgG4-positive plasma cell counts ranged between 0 and 88 (mean 24) and the IgG4/IgG ratios ranged between 0 and 0.51 (mean 0.22). Taken by histological subtype, IgG4-positive plasma cell counts averaged 34 cells/hpf and 6 cells/hpf for squamous cell carcinomas (figure 2G–I) and adenocarcinomas (figure 2J–L), respectively. In squamous cell carcinomas, 1–81 IgG4-positive plasma cells/hpf were detected. The samples from adenocarcinomas contained between 0 and 88 IgG4-positive plasma cells/hpf. The average IgG4/IgG ratio was similar in squamous cell

Figure 3 Box plot of absolute IgG4 plasma cell counts per hpf. The maximum outlier in each group is represented by a star. Horizontal lines represent thresholds for the diagnosis of IgG4-associated sclerosing disease (in particular autoimmune pancreatitis) defined in previous publications (reference number in parentheses).

carcinoma and adenocarcinoma cases (0.23 vs 0.21 respectively, range 0–0.51 for squamous cell carcinoma and 0–0.48 for adenocarcinomas). There was no statistically significant difference between both the absolute IgG4 plasma cell counts ($p=0.082$) and the IgG4/IgG ratios ($p=0.79$) regarding the groups of squamous cell carcinoma and adenocarcinoma.

DISCUSSION

This study is the first to address the issue of IgG4-positive plasma cells in diverse common non-specific chronic inflammatory conditions from different anatomical sites. Although the number of evaluated cases is relatively low for some included entities, our collective results clearly demonstrate a greatly varied ubiquitous presence of IgG4 plasma cells as a component of ordinary non-specific chronic inflammatory conditions from different organ systems. The IgG4 plasma cell counts varied from very low and absent to significantly high numbers exceeding 100 IgG4-positive plasma cells/hpf in some lesions. The mean IgG4/IgG ratios varied between 0.02 and 0.4. These results raise several questions with regard to (1) IgG4 plasma cells as an ubiquitous 'physiological' component of ordinary inflammation; (2) the potential role for IgG4 plasma cells in the pathogenesis of some autoimmune diseases such as rheumatoid arthritis where high IgG4 plasma cell counts are fairly common; (3) the presence of localised tumefactive IgG4-rich inflammatory lesions unrelated to systemic disease as a variant of inflammatory pseudotumour as depicted here by oral lesions; and (4) the questionable reliability of numerical cut-off values as an adjunct to the clinical diagnosis of ISD.

Our data show that variable numbers of IgG4-positive plasma cells represent a common constituent of chronic inflammation. The numbers of these IgG4 plasma cells varied greatly from one lesion to another at the same anatomical sites and also among lesions from different organ systems. The count of IgG4 plasma cells in chronic obstructive (non-autoimmune) sialadenitis

related to sialolithiasis was significantly lower than that reported for the autoimmune (IgG4-related) sclerosing sialadenitis/Küttner tumour in the current and previous studies^{10 11} with IgG4/IgG ratios of 0.02 versus 0.59 in our study. Similarly, the absolute IgG4 counts were significantly different in the two aetiological groups (3 vs 40/hpf). These findings underscore the value of the IgG4/IgG ratio and IgG4 count in this differential diagnosis in the salivary glands.

Cases of rheumatoid synovitis contained generally high but variable numbers of IgG4 plasma cells in this study. The degree to which the variation among individual patients with rheumatoid disease is due to anti-inflammatory treatment or possibly to differences in the levels of disease activity remains unclear. In the cases of synovitis without a clinical diagnosis of rheumatoid arthritis, the IgG4 counts per hpf and IgG4/IgG ratios were significantly lower ($p=0.026$). These results suggest that an increased number of IgG4-positive plasma cells may be a finding specific to rheumatoid synovitis. Of the 15 cases of non-specific synovitis, three cases showed infiltrates of IgG4-positive plasma cells in excess of 30 IgG4-positive plasma cells/hpf. Careful re-evaluation of these samples showed a histomorphological picture compatible with rheumatoid disease in one case. However, clinical data regarding rheumatoid arthritis were inconclusive, and an infectious aetiology could not be definitely excluded in these cases. Unfortunately, we were not able to correlate our findings with serum IgG4, as this parameter is not measured routinely in most patients. Lin *et al* showed IgG4 serum levels to be elevated in patients with rheumatoid arthritis.²⁹ Furthermore, Engelmann *et al* demonstrated that IgG4 significantly outweighs IgG2 and IgG3 among anticyclic citrullinated peptides (anti-CCP) antibodies in rheumatoid arthritis.³⁰ Our current data indicate that IgG4-positive plasma cells are numerous in the synovial tissues of patients with rheumatoid arthritis and may thus be involved in the pathogenesis of this disease. However, further research based on larger

Figure 4 Box plot of IgG4/IgG ratios. The maximum outlier in each group is represented by a star. Horizontal lines represent thresholds for the diagnosis of ISD defined in previous publications (reference number in parentheses).

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case series with a careful correlation of histopathological, clinical and serological data is needed to further substantiate this hypothesis.

Localised oral inflammatory lesions represent another subgroup with significant numbers of IgG4-positive plasma cells in this study. Using elispot immunoassays, Ogawa *et al* demonstrated that IgG4 expressing plasma cells are present in inflamed gingival tissue and documented a rise in IgG4 expression when comparing moderate parodontitis with advanced parodontitis.³¹ However, no detailed histopathological data are currently available regarding IgG4-positive plasma cells in gingival tissues. Our results suggest that lesions of the oral cavity may represent a variant of IgG4-rich localised inflammatory pseudotumour (inflammatory tumefactive lesion) unrelated to ISD. Interestingly, a recent study has described similar IgG4 plasma cell-rich localised tumefactive fibrous lesions in the gastrointestinal tract²⁰ and the larynx,³² most of which were not associated with autoimmune systemic disease.

In this study, we found low numbers of IgG4 expressing plasma cells in the inflammatory infiltrates of Crohn disease and ulcerative colitis compared with sigmoid diverticulitis. Ravi *et al* hypothesised that the presence of IgG4-positive plasma cells in chronic inflammatory bowel disease may indicate an association with ISD and may thus represent a further extrapancreatic manifestation of AIP.³³ However, the authors considered a number of 10 IgG4-positive plasma cells/hpf an 'increased infiltrate.' Our results showed both very low counts and counts in excess of 10 plasma cells in Crohn disease and ulcerative colitis, suggesting an even wider range of IgG4-positive plasma cells, most probably as a usual inflammatory cell component and not necessarily as an indication for a central role of IgG4 plasma cells in the pathogenesis of chronic inflammatory bowel disease. However, more extended future studies are needed to elucidate this matter further.

The analysis of eight cases of chronic inflammation in the skin yielded interesting results. We counted high numbers of IgG4-positive plasma cells in unguis incarnatus (120/hpf) as well as in non-specific posthitis. In contrast, lichen sclerosus cases showed uniformly low numbers of IgG4-positive plasma cells (mean 2/hpf). It is well known that serum IgG4 levels are elevated in patients with allergic symptoms and atopic dermatitis.³⁴ Also, in pemphigus the autoantibodies belong mainly to the IgG4 and IgG1 subclasses.³⁵ Our results show a great variation in the density of IgG4 plasma cells in our small group of non-specific chronic inflammatory skin lesions, thus underscoring the

necessity of careful interpretation of skin biopsy when looking for histological evidence of ISD.

In addition, we demonstrated that IgG4 plasma cells also represent a variable component of peritumoral/intratumoral inflammatory response to carcinomas of various types and locations. Again our results underscore the need to proceed with caution when the IgG4-positive plasma cell infiltration is used to differentiate between neoplasia and mass forming ISD. Our results showed up to 11 IgG4-positive plasma cells/hpf in pancreas specimens harbouring ductal adenocarcinoma. This is in accordance with a recent study by Dhall *et al* who showed that in peritumoral pancreatitis, up to 50 IgG4-positive plasma cells may be present per hpf.²⁵ The presence of IgG4-positive plasma cells should therefore be considered suggestive of, but not necessarily diagnostic of, AIP. Other diagnostic criteria (imaging findings, serum IgG4 levels, typical histology) should always be taken into consideration in this context.

Our results clearly show that the number of IgG4-positive plasma cell infiltrates in plasma cell-rich inflammations from different locations and aetiologies may easily exceed the thresholds defined in the literature for ISD (figures 3, 4). The numbers of IgG4-positive plasma cells in diverse common inflammatory conditions vary greatly depending on localisation and aetiology. Our results demonstrate how difficult it would be to try to establish a universally valid threshold for 'significant IgG4 plasma cell count' for diagnosis of ISD disorders. Also, it is evident from our results that a threshold would not be suitable for all organ systems and that more extended studies are needed to try to define an organ-specific cut-off value for diagnosis of the different subsets of ISD. The presence of a tumefactive inflammatory infiltrate with prominent accompanying sclerosis and obliterative phlebitis are of particular importance when rendering a diagnosis of ISD. The plasma cell counts should be interpreted cautiously in the context of these typical histopathological features, thereby taking the serum IgG4 levels and other clinical findings (particularly the presence of similar manifestation in other organ systems) into consideration.

Competing interests None.

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REFERENCES

1. Bateman AC, Deheragoda MG. IgG4-related systemic sclerosing disease—an emerging and under-diagnosed condition. *Histopathology* 2009;**55**:373–83.
2. Cheuk W, Lee KC, Chong LY, *et al*. IgG4-related Sclerosing disease: a potential new etiology of cutaneous pseudolymphoma. *Am J Surg Pathol* 2009;**33**:1713–19.
3. Kamisawa T, Okamoto A. IgG4-related sclerosing disease. *World J Gastroenterol* 2008;**14**:3948–55.
4. Masaki Y, Dong L, Kurose N, *et al*. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis* 2009;**68**:1310–15.
5. Chari ST, Smyrk TC, Levy MJ, *et al*. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. *Clin Gastroenterol Hepatol* 2006;**4**:1010–16; quiz 934.
6. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol* 2006;**41**:613–25.
7. Yoshida K, Toki F, Takeuchi T, *et al*. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 1995;**40**:1561–8.
8. Zhang L, Smyrk TC. Autoimmune pancreatitis and IgG4-related systemic diseases. *Int J Clin Exp Pathol* 2010;**3**:491–504.
9. Alderlieste YA, van den Elzen BD, Rauws EA, *et al*. Immunoglobulin G4-associated cholangitis: one variant of immunoglobulin G4-related systemic disease. *Digestion* 2009;**79**:220–8.
10. Geyer JT, Ferry JA, Harris NL, *et al*. Chronic sclerosing sialadenitis (Kuttner tumor) is an IgG4-associated disease. *Am J Surg Pathol* 2010;**34**:202–10.
11. Kitagawa S, Zen Y, Harada K, *et al*. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner's tumor). *Am J Surg Pathol* 2005;**29**:783–91.
12. Takahira M, Kawano M, Zen Y, *et al*. IgG4-related chronic sclerosing dacryoadenitis. *Arch Ophthalmol* 2007;**125**:1575–8.

Take-home messages

- IgG4-positive plasma cells constitute a common component of the inflammatory infiltrates in non-specific, non-ISD related chronic inflammatory lesions of different localisations.
- The intensity of IgG4-positive plasma cells in non-specific inflammation varies greatly depending on the lesion type and site.
- The ubiquity and the wide range of IgG4-positive plasma cells in non-specific chronic inflammation largely limit the establishment of a universally valid threshold of IgG4-positive plasma cell count for diagnosis of ISD.
- IgG4 plasma cells may play a role in the pathogenesis of rheumatoid synovitis and oral inflammatory lesions.

13. **Zen Y**, Onodera M, Inoue D, *et al*. Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. *Am J Surg Pathol* 2009;**33**:1833–9.
14. **Diebold J**, Le Tourneau A, Marmey B, *et al*. Is sclerosing angiomatoid nodular transformation (SANT) of the splenic red pulp identical to inflammatory pseudotumour? Report of 16 cases. *Histopathology* 2008;**53**:299–310.
15. **Cornell LD**, Chicano SL, Deshpande V, *et al*. Pseudotumors due to IgG4 immune-complex tubulointerstitial nephritis associated with autoimmune pancreatocentric disease. *Am J Surg Pathol* 2007;**31**:1586–97.
16. **Cheuk W**, Yuen HK, Chu SY, *et al*. Lymphadenopathy of IgG4-related sclerosing disease. *Am J Surg Pathol* 2008;**32**:671–81.
17. **Shimatsu A**, Oki Y, Fujisawa I, *et al*. Pituitary and stalk lesions (infundibulo-hypophysitis) associated with immunoglobulin G4-related systemic disease: an emerging clinical entity. *Endocr J* 2009;**56**:1033–41.
18. **Inoue M**, Nose N, Nishikawa H, *et al*. Successful treatment of sclerosing mediastinitis with a high serum IgG4 level. *Gen Thorac Cardiovasc Surg* 2007;**55**:431–3.
19. **Zen Y**, Inoue D, Kitao A, *et al*. IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. *Am J Surg Pathol* 2009;**33**:1886–93.
20. **Chetty R**, Serra S, Gauchotte G, *et al*. Sclerosing nodular lesions of the gastrointestinal tract containing large numbers of IgG4 plasma cells. *Pathology* 2011;**43**:31–5.
21. **Deheragoda MG**, Church NI, Rodriguez-Justo M, *et al*. The use of immunoglobulin g4 immunostaining in diagnosing pancreatic and extrapancreatic involvement in autoimmune pancreatitis. *Clin Gastroenterol Hepatol* 2007;**5**:1229–34.
22. **Detlefsen S**, Mohr Drewes A, Vyberg M, *et al*. Diagnosis of autoimmune pancreatitis by core needle biopsy: application of six microscopic criteria. *Virchows Arch* 2009;**454**:531–9.
23. **Kloppel G**, Sipos B, Zamboni G, *et al*. Autoimmune pancreatitis: histo- and immunopathological features. *J Gastroenterol* 2007;**42**(Suppl 18):28–31.
24. **Kojima M**, Sipos B, Klapper W, *et al*. Autoimmune pancreatitis: frequency, IgG4 expression, and clonality of T and B cells. *Am J Surg Pathol* 2007;**31**:521–8.
25. **Dhall D**, Suriawinata AA, Tang LH, *et al*. Use of immunohistochemistry for IgG4 in the distinction of autoimmune pancreatitis from peritumoral pancreatitis. *Hum Pathol* 2010;**41**:643–52.
26. **Chen TS**, Montgomery EA. Are tumefactive lesions classified as sclerosing mesenteritis a subset of IgG4-related sclerosing disorders? *J Clin Pathol* 2008;**61**:1093–7.
27. **Kamisawa T**, Funata N, Hayashi Y, *et al*. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;**38**:982–4.
28. **Zen Y**, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. *Am J Surg Pathol* 2010;**34**:1812–19.
29. **Lin G**, Li J. Elevation of serum IgG subclass concentration in patients with rheumatoid arthritis. *Rheumatol Int* 2010;**30**:837–40.
30. **Engelmann R**, Brandt J, Eggert M, *et al*. IgG1 and IgG4 are the predominant subclasses among auto-antibodies against two citrullinated antigens in RA. *Rheumatology (Oxford)* 2008;**47**:1489–92.
31. **Ogawa T**, Tarkowski A, McGhee ML, *et al*. Analysis of human IgG and IgA subclass antibody-secreting cells from localized chronic inflammatory tissue. *J Immunol* 1989;**142**:1150–8.
32. **Volker HU**, Scheich M, Zettl A, *et al*. Laryngeal inflammatory myofibroblastic tumors: Different clinical appearance and histomorphologic presentation of one entity. *Head Neck* 2010;**32**:1573–8.
33. **Ravi K**, Chari ST, Vege SS, *et al*. Inflammatory bowel disease in the setting of autoimmune pancreatitis. *Inflamm Bowel Dis* 2009;**15**:1326–30.
34. **Merrett J**, Barnetson RS, Burr ML, *et al*. Total and specific IgG4 antibody levels in atopic eczema. *Clin Exp Immunol* 1984;**56**:645–52.
35. **Sitaru C**, Mihai S, Zillikens D. The relevance of the IgG subclass of autoantibodies for blister induction in autoimmune bullous skin diseases. *Arch Dermatol Res* 2007;**299**:1–8.

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