Needle Biopsy Compared With Surgical Biopsy: Pitfalls of Small Biopsy in Histological Diagnosis of IgG4-related Disease

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Abstract

Objective
The growing utilization of needle biopsy has challenged the current pathology consensus of IgG4-related disease (IgG4-RD). The aims of this study were to identify the histological characteristics of needle biopsy and surgical specimens, and evaluate the ability of needle biopsy in histological diagnosis of IgG4-RD.

Methods
Biopsies from patients who were referred to as IgG4-RD by the 2019 ACR/EULAR IgG4-RD classification criteria in Peking University People’s Hospital from 2012 to 2019 were re-evaluated. Typical histological features and diagnostic categories were compared between needle biopsy and surgical biopsy.

Results
In total, 69 patients met the 2019 ACR/EULAR classification criteria and 72 biopsies of them were re-evaluated. All cases showed lymphoplasmacytic infiltrate, while storiform fibrosis and obliterative phlebitis were only present in 35 (48.6%) and 23 (31.9%) specimens, respectively. Storiform fibrosis was more likely to be seen in retroperitoneum lesion ($P=0.033$). Surgical biopsy showed significantly higher IgG4+ plasma cells/high power field (IgG4/HPF) count ($P<0.01$) and higher proportion of IgG4/HPF>10 ($P<0.01$). No significant difference was observed with regard to the ratio of IgG4+/IgG+ cells (IgG4/IgG) ($P=0.399$), storiform fibrosis ($P=0.739$), and obliterative phlebitis ($P=0.153$). According to the 2011 comprehensive diagnostic criteria, patients who performed a needle biopsy were less likely to be probable IgG4-RD ($P=0.045$). Based on the 2011 pathology consensus, needle biopsy was tougher to be diagnosed as IgG4-RD ($P<0.01$), especially to be highly suggestive IgG4-RD ($P<0.01$). Only 1/18 (5.6%) needle salivary specimens fulfilled the cutoff of IgG4/HPF>100, which was significantly less than 15/23 (65.2%) of surgical ones ($P<0.01$).

Conclusions
Needle biopsy shows an inferiority in detecting IgG4/HPF count but not in IgG4/IgG ratio, storiform fibrosis and obliterative phlebitis. Compared with surgical samples, it is tougher for needle biopsy to obtain a histological diagnosis of IgG4-RD. A different IgG4/HPF threshold for needle biopsy of salivary glands may be considered.

Introduction
IgG4-related disease (IgG4-RD) is a newly recognized fibroinflammatory condition characterized by tumefactive lesions involved in multiple sites; often but not always, the elevated serum IgG concentration; and a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells$^[1]$. Comprehensive diagnostic criteria were established in 2011, dividing IgG4-RD into possible, probable and
definite cases based on the clinical, serological and pathological evidence\textsuperscript{[2]} (Supplementary Table 1). At the same time, a pathology consensus for IgG4-RD was published for histopathological diagnosis based on histological traits and immunohistochemical features\textsuperscript{[3]} (Supplementary Table 2). Despite the importance of biopsy in excluding many mimickers, biopsy is not always easily accessible or acceptable by patients in many cases. In the context of that, the 2019 ACR/EULAR classification criteria were codified, allowing the judgement of IgG4-RD in the absence of a biopsy\textsuperscript{[4]}. Nevertheless, the complexity has constrained the utilization of the classification criteria for clinical purpose. Therefore, comprehensive diagnostic criteria that largely depend on pathology are still dispensible in clinical practice. Recently, amplified utilization of needle biopsy has been challenging the pathology consensus since current pathology recommendations are largely based on resection specimens\textsuperscript{[5]}. However, to the best of our knowledge, there have been no studies comparing the ability of needle biopsy and open surgical biopsy in overall IgG4-RD spectrum. And few literatures have re-evaluated the 2011 pathology consensus.

We performed a comparison of needle biopsy and surgical biopsy in terms of histological features and diagnostic categories, and re-evaluated the 2011 pathology consensus based on 72 biopsied specimens (either needle or surgical biopsy) from 69 patients who underwent biopsy and were referred to as IgG4-RD by the 2019 ACR/EULAR IgG4-RD classification criteria in Peking University People’s Hospital from 2012 to 2019\textsuperscript{[4]}. The aim of this study was to identify the histological characteristics of different biopsy specimens and evaluate the diagnostic ability of needle biopsy.

**Materials And Methods**

Patients who underwent biopsy (either needle biopsy or surgical resection) in Peking University People’s Hospital and were histopathologically suggested or suspected as IgG4-RD from 2012 to 2019 were enrolled. All patients provided written informed consent. The following data were collected from the medical records: gender, age of disease onset and baseline serum IgG4 concentration.

Two pathologists who were blind to the sample information worked independently and re-evaluated the hematoxylin and eosin (H&E)–stained, IgG4 and IgG stained slides of enrolled patients. The degree of fibrosis and lymphoplasmacytic infiltrates was assessed. Typical histopathological characteristics of storiform fibrosis and obliterative phlebitis were recorded. Three 40 × fields with the highest number of IgG4 plasma cells were calculated and the average number was recorded. The same three fields were counted for the IgG4/IgG ratio\textsuperscript{[2,3]}. In cases where the pathologists disagreed, specimens were evaluated in tandem and a diagnosis was assigned based on consensus. Cases would be excluded when a consensus could not be reached. Thereafter, criteria score were calculated based on the clinical, serological and pathological evidence according to the 2019 ACR/EULAR classification criteria. Cases who failed to meet the classification criteria with a score less than 20 were excluded.

Quantitative variables with non-normally distribution were presented as medians and interquartile range (IQR), and were compared with Mann-Whitney test. Quantitative variables with normally distribution were presented as Mean ± Standard Deviation (SD), and were compared with Student’s $t$-test. Categorical
variables were assessed with the Chi square test or Fisher's exact test, as appropriate. \( P \)-values were adjusted with Bonferroni method when comparing multiple categorical variables in pairs. \( P \)-values < 0.05 were considered statistically significant. All statistical analyses were performed by SPSS version 25.0. All figures were made by the Origin 2018.

This study was approved by the Medical Ethics Committee of Peking University People's Hospital (Beijing, China).

Results

Clinical characteristics of the 69 patients and pathological features of the 72 specimens

In total, 69 patients met the 2019 ACR/EULAR criteria, whose classification criteria scores were all above 20 and the median score was 39.5 (31.3, 47.3). 44 of the 69 patients (61.1%) were males and the median age were 56.0 (50.3, 64.0). Three of the 69 patients underwent two biopsies of different organs and 72 specimens in all were re-evaluated (Table 1).

Table 1 Clinical and pathological characteristics of the patients
| Characteristics                              | Value                                           |
|---------------------------------------------|------------------------------------------------|
| Age, Median (IQR)                           | 56.0 (50.3, 64.0)                              |
| Gender, Male, n (%)                         | 44 (61.1)                                      |
| Serum IgG4 (mg/dl), Median (IQR)            | 770.0 (230.8, 1870.0)                         |
| Serum IgG4, n (%)                           |                                                |
| < 1 ULN                                     | 14 (19.4)                                      |
| 1~2 ULN                                     | 11 (15.3)                                      |
| 2~5 ULN                                     | 14 (19.4)                                      |
| ≥ 5 ULN                                     | 32 (44.4)                                      |
| Missing Value                               | 1 (1.4)                                        |
| Biopsy method, n (%)                        |                                                |
| Needle biopsy                               | 24 (33.3)                                      |
| Surgical biopsy                             | 48 (66.7)                                      |
| Biopsy organ, n (%)                         |                                                |
| Meningus                                    | 1 (1.4)                                        |
| Lacrimal gland                              | 6 (8.3)                                        |
| Salivary gland                              | 41 (56.9)                                      |
| Lymph node                                  | 8 (11.1)                                       |
| Lung                                        | 2 (2.8)                                        |
| Pleura                                      | 1 (1.4)                                        |
| Pancreas                                    | 2 (2.8)                                        |
| Bile duct                                   | 1 (1.4)                                        |
| Retroperitoneum                             | 9 (12.5)                                       |
| Prostate                                    | 1 (1.4)                                        |
| IgG4/HPF, Median (IQR)                      | 80.0 (50.0, 130.0)                             |
| IgG4/HPF, n (%)                             |                                                |
| > 10                                        | 66 (91.7)                                      |
| ≤ 10                                        | 3 (4.2)                                        |
| Indetermined                                | 3 (4.2)                                        |
| IgG4/IgG (%) | Mean ± SD |
|-------------|-----------|
| 67.5 ± 23.3 |

| IgG4/IgG, n (%) |
|----------------|
| > 40% | 62 (86.1) |
| ≤ 40% | 9 (12.5) |
| Indetermined | 1 (1.4) |

| Lymphoplasmacytic infiltrate | 72 (100.0) |
| Storiform fibrosis, n (%) | 35 (48.6) |
| Obliterative phlebitis, n (%) | 23 (31.9) |

| 2019 ACR/EULAR Criteria Score, Median (IQR) |
|--------------------------------------------|
| 39.5 (31.3, 47.3) |

| 2011 Comprehensive Diagnostic Criteria, n (%) |
|----------------------------------------------|
| Possible | 11 (15.3) |
| Probable | 14 (19.4) |
| Definite | 47 (65.3) |

| 2011 Pathology Diagnostic Consensus, n (%) |
|-------------------------------------------|
| Insufficient | 30 (41.7) |
| Probable | 18 (25.0) |
| Highly Suggestive | 24 (33.3%) |

Salivary gland (41/72, 56.9%) was the most common site of biopsy. Other involved organs included retroperitoneum (9/72, 12.5%), lymph nodes (8/72, 11.1%), lacrimal gland (6/72, 8.3%), lung (2/72, 2.8%), pancreas (2/72, 2.8%), meningus (1/72, 1.4%), pleura (1/72, 1.4%), bile duct (1/72, 1.4%), and prostate (1/72, 1.4%). According to the 2011 comprehensive diagnostic criteria, 11 (15.3%) of the patients were possible, 14 (19.4%) were probable and 47 (65.3%) were definite IgG4-RD. For patients who performed two biopsies, the diagnostic categories were identical. According to the 2011 pathology consensus, 30 (41.7%) of the biopsies were insufficient, 18 (25.0%) were probable and 24 (33.3%) were highly suggestive IgG4-RD (Table 1).

Dense lymphoplasmacytic infiltrate was ubiquitous regardless of the biopsy sites or methods. The median IgG4/HPF count was 80.0 (50.0, 130.0) and the average IgG4/IgG ratio was 67.5 ± 23.3%. Retroperitoneum specimen tended to show less IgG4/HPF count than other organs, even though no significant difference was found ($P = 0.177$). 62 (86.1%) and 66 (91.7%) biopsies showed IgG4/IgG > 40% and IgG4/HPF > 10, respectively. Storiform fibrosis and obliterative phlebitis were comparatively uncommon and were only present in 35 (48.6%) and 23 (31.9%) specimens, respectively (Table 1). No organ specificity of obliterative phlebitis was observed among different organs ($P = 0.446$), while
storiform fibrosis was more likely to be seen in retroperitoneum lesion \((P = 0.033)\) (Fig. 3, Supplementary Table 4).

**Needle biopsy versus surgical biopsy**

48/72 (66.7%) specimens were surgical biopsy (Supplementary Table 2). No significant discrepancy was found between needle biopsy and surgical biopsy in terms of IgG4+/IgG + cells ratio \((\text{IgG4/IgG})\) \((P = 0.438)\), proportion of \(\text{IgG4/IgG} > 40\%\) \((P = 0.399)\), storiform fibrosis \((P = 0.739)\) and obliterative phlebitis \((P = 0.153)\). However, needle specimens tended to show significantly less IgG4/HPF count \((P = 0.003)\) and lower proportion of \(\text{IgG4/HPF} > 10\) \((P = 0.001)\) than needle biopsy. Compatible with that, according to the 2011 comprehensive diagnostic criteria, patients who performed a needle biopsy were less likely to be probable IgG4-RD \((P = 0.045)\) while serum IgG4 showed no significant difference \((P = 0.618)\). Consistently, based on the 2011 pathology consensus, needle biopsy was tougher to be histologically identified as IgG4-RD \((P < 0.001)\), especially to be highly suggestive IgG4-RD \((P < 0.001)\) (Fig. 1, Supplementary Table 3). These data suggested that needle biopsy might be less capable to capture full IgG4 profile and thus insufficient IgG4/HPF count, which led to less possibility of histological identification based on the 2011 pathology consensus statement.

**Re-evaluation of 2011 pathology consensus**

According to the 2011 pathology consensus, 24 of the 72 IgG4-RD (33.33%) were highly suggestive, 18 (25.00%) were probable, and 30 (41.67%) were insufficient to be histologically identified as IgG4-RD. Given that all the 72 specimens showed at least one of the three pathological features (lymphoplasmacytic infiltrate), all of these insufficient biopsies failed to fulfill either required IgG4/HPF cut-off point or IgG4/IgG > 40%. Even though IgG4/HPF > 10 had been proposed as one component of a comprehensive diagnostic panel, the pathology criteria recommended a set of IgG4/HPF threshold that was specific to each organ, from 10 to 200. In the 30 (41.67%) insufficient IgG4-RD specimens, 7 (9.72%) showed IgG4/IgG \(\leq 40\%\) and 29 (40.28%) showed less IgG4/HPF count than the cut-off value as recommended by the consensus (Table 2).

Table 2 Histological Diagnosis according to 2011 pathological consensus of 72 IgG4-RD specimens
|                          | n^a | N^b | n/72^c (%) | n/N^d (%) |
|--------------------------|-----|-----|------------|-----------|
| Highly suggestive        | 24  | -   | 33.33      | -         |
| Probable                 | 18  | -   | 25.00      | -         |
| Insufficient             | 30  | -   | 41.67      | -         |
| IgG4/IgG < 40%           | 7   | -   | 9.72       | -         |
| Salivary gland           | 4   | 41  | 5.55       | 9.76      |
| Retroperitoneum          | 1   | 9   | 1.39       | 11.11     |
| Lymph node               | 1   | 8   | 1.39       | 12.50     |
| Pancreas                 | 1   | 2   | 1.39       | 50.00     |
| IgG4/HP < cut-off value  | 29  | -   | 40.28      | -         |
| Salivary gland           | 23  | 41  | 31.94      | 56.10     |
| Lymph node               | 2   | 8   | 2.78       | 25.00     |
| Lung                     | 1   | 2   | 1.39       | 50.00     |
| Lacrimal gland           | 1   | 6   | 1.39       | 16.67     |
| Pleura                   | 1   | 1   | 1.39       | 100.00    |
| Pancreas                 | 1   | 2   | 1.39       | 50.00     |

^a n represents the number of cases

^b N represents the number of biopsies taken from the same organ

^c Proportion in all the 72 biopsies

^d Proportion in all biopsies of the same organ

In the 29 (40.28%) specimens with insufficient IgG4/HPF count, 23 (31.94%) were taken from salivary glands, 2 (2.78%) were from lymph nodes, and 1 (1.39%) was from lung, lacrimal gland, pleura and pancreas, respectively. The cut-off IgG4/HPF value of salivary gland recommended by the pathology consensus was 100/HPF. Nevertheless, in this cohort, only 18 out of 41 (43.90%) salivary samples had met this threshold, and 17 of them were surgical specimens while only 1 was needle biopsy (Table 2). To identify the effect of biopsy methods, salivary gland specimens were subgrouped according to whether it was a needle biopsy or a surgical biopsy (Fig. 2).

Consistent with the results above, surgical biopsy tended to show significantly higher IgG4/HPF count (P < 0.01) in salivary samples. No more than 1/18 (5.6%) needle salivary specimens met the cut-off value of
IgG4/HPF > 100, which was significantly less than 15/23 (65.2%) of surgical ones ($P < 0.01$). Additionally, needle biopsy was more likely to be neither highly suggestive nor probable IgG4-RD ($P < 0.01$). These data suggested that, compared with surgical biopsy, it was much tougher for needle biopsy to capture enough IgG4/HPF count and thus to be judged as IgG4-RD in salivary glands (Fig. 2).

**Discussion**

IgG4-RD is a chronic mass-forming fibroinflammatory disease that may be involved in multiple organs. Typical histopathological features of IgG4-RD include dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis. In this study, biopsy of IgG4-RD lesions ubiquitously showed lymphoplasmacytic infiltrate, but often lacking either storiform fibrosis or obliterative phlebitis. Furthermore, needle biopsy proved to be less capable of detecting IgG4/HPF count and was much tougher to be identified as IgG4-RD, especially in salivary gland lesions.

Storiform fibrosis and obliterative phlebitis are two typical features of IgG4-RD, and the histological appearance of them usually show high specificity. However, in this study, merely 48.6% biopsies showed the storiform fibrosis and obliterative phlebitis were only present in 31.9% samples. Moreover, organ-specific differences including the absence of storiform fibrosis within lacrimal glands and lymph nodes, and the lower frequency of obliterative phlebitis in salivary glands, lymph nodes and retroperitoneum were also observed. These results were in line with the previous studies$^{[6,7]}$. Furthermore, even though no significant discrepancy was found in this study, it had been suggested that storiform fibrosis and obliterative phlebitis might be scarcely detected in small samples such as needle biopsy$^{[3,8]}$. These results suggest the importance of IgG4/HPF count and IgG4/IgG ratio in the judgement of IgG4-RD specimens when the storiform fibrosis and obliterative phlebitis are absent.

In the IgG4-RD pathology consensus, 3-tiered terminology (insufficient, probable and highly suggestive) were endorsed for the histopathological judgement based on the three histological features (lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis), and immunohistochemical features (ratio of IgG4/IgG and IgG4/HPF count). In our cohort, nearly half of salivary specimens were defect of enough IgG4/HPF count for histological identification. Similarly, Andrew et al reported that two thirds of lacrimal IgG4-RD cases failed to be diagnosed using a cutoff of IgG4/HPF > 100 as recommended by the consensus, but difference between needle biopsy and surgical samples was not explored$^{[9]}$. Even though some researchers have suggested performing a salivary gland biopsy when IgG4-related disease is suspected$^{[10,11]}$, in this study, however, most of the insufficient salivary samples were biopsied by needle, while most surgical samples still met the threshold of IgG4/HPF > 100. Indeed, in the 2011 pathology consensus, biopsy samples in organs like lung, pancreas, bile duct, liver and kidney have lower IgG4/HPF threshold than that of surgical ones. While the cutoff of IgG4/HPF count for other organs including salivary gland, lacrimal gland, lymph node, pleura, retroperitoneum, aorta and skin suggested by the consensus, as we have observed, are more suitable to surgical samples but may be less applicable to the small biopsy$^{[3,12]}$. It is noteworthy that setting the cutoff to IgG4/HPF > 10, surgical
cases that meet this threshold are still significantly more than needle biopsies. Therefore, we suggest the superiority of surgical samples in a suspicious IgG4-RD salivary lesion. And a distinctive cut-off IgG4/HPF count other than 100/HPF for needle biopsy of salivary gland may be considered.

The major issue of needle biopsy is represented by the inadequacy of the material obtained for histopathological evaluation and immunohistochemical tests, and thus incomplete characterization of a lymphoproliferative disorder\textsuperscript{[13,14]}. Besides, plasma cells crushed by an artifact tend to cause unsuccessful immunostaining in smaller samples\textsuperscript{[15]}. The quality of a needle biopsy might also depend on the experience of the operator, the number of cores obtained from the lesion, the gauge of the needle we used and the ultrasound direction\textsuperscript{[16]}. However, needle biopsy still has some advantages. Compared with surgical resection, needle biopsy is less invasive, less expensive, and usually with fewer long-term or transient complications, which have a high impact on the patient’s acceptance, especially when the biopsy of an internal viscera is needed. Moreover, even though open surgical biopsies allowed the adequate material for pathological evaluation, it is a non-targeted approach. Regions with restricted lesions may not represent the full features of the disorder. In contrast, ultrasound-guided needle biopsy is able to distinguish areas with different sonographic patterns and target the most suspicious lesions\textsuperscript{[16]}. In addition, whenever any kind of neoplasm is possible, open biopsy is contraindicated since it may compromise patients’ outcome (e.g. by increasing the risk of tumor recurrence)\textsuperscript{[17,18]}. Improving the specificity of the pathology criteria by setting high organ-specific cutoffs for IgG4 staining is absolutely necessary. What should be emphasized is that we do not interpret a lower IgG4 cutoff for salivary specimens, but consider a different threshold for needle biopsy. It remains to figure out whether needle biopsy is feasible or not for the diagnosis of IgG4-RD and if a different IgG4/HPF cutoff for needle biopsy might impair the specificity. Last but not least, despite the importance of pathology, additional clinical, serological and radiological evidence is still indispensible for confirming the ultimate diagnosis of IgG4-RD. Patients who lacked one or more of the histological and immunohistochemical features of IgG4-RD may overlap with those showing definite features with regard to serum IgG4 levels, multiorgan involvement, and response to glucocorticoids therapy\textsuperscript{[5]}. Even cases classified in the pathological category of insufficient IgG4-RD do not exclude the diagnosis thoroughly. For highly suggestive cases, the pathology criteria might not be infallible, either\textsuperscript{[19,20]}. Potential reasons might include sampling artifact, the effects of previous therapy, and progression to a fibrotic stage, etc\textsuperscript{[3]}. One limitation of this study is that, the cohort of this study does not cover all the common lesions of IgG4-RD, and most of the samples come from salivary glands. Therefore, it is still unable to validate whether surgical biopsy is superior to needle biopsy with regard to calculating IgG4/HPF count in other organs.

**Conclusions**
In conclusion, needle biopsy shows an inferiority in detecting IgG4/HPF count but not in IgG4/IgG ratio, storiform fibrosis and obliterative phlebitis. Compared with surgical samples, it is tougher for needle biopsy to obtain a histological diagnosis of IgG4-RD. A different IgG4/HPF threshold for needle biopsy of salivary glands may be considered.

**Abbreviations**

| Abbreviation | Definition                        |
|--------------|----------------------------------|
| IgG4-RD      | IgG4-related disease             |
| IgG4/HPF     | IgG4+ plasma cells/high power field |
| IgG4/IgG     | the ratio of IgG4+/IgG+ cells    |
| H&E          | Hematoxylin and eosin            |
| IQR          | Interquartile range              |
| SD           | Standard deviation               |

**Declarations**

**Ethical Approval and Consent to participate**

This study was approved by the Medical Ethics Committee of Peking University People's Hospital (Beijing, China). All patients provided written informed consent for the utilization of their medical materials.

**Consent for publication**

All authors gave their consent to publication of this manuscript.

**Availability of supporting data**

Not applicable.

**Competing interests**

The authors have no conflicts of interest to disclose.

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**Authors’ contributions**
All authors participated in the analyses and interpretation of data, wrote or critically reviewed the manuscript, and reviewed and approved the final version.

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