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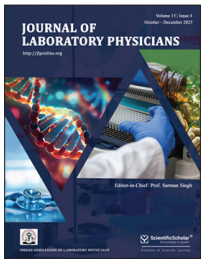

Original Article

Utility of immunohistochemistry for immunoglobulin G4 in the diagnosis of pemphigus

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ABSTRACT

Objectives: Direct immunofluorescence (DIF) is the diagnostic gold standard for pemphigus. However, it is limited by the requirement of additional fresh-frozen tissue, immediate processing, and availability of a fluorescent microscope. The present study aims to assess the role of immunoglobulin G4 (IgG4) immunohistochemistry (IHC) on formalin-fixed paraffin-embedded tissue for the diagnosis of pemphigus by comparing IgG4-IHC results to DIF.

Materials and Methods: IgG4-IHC was performed on formalin-fixed paraffin-embedded sections of lesional and perilesional skin biopsies of 30 cases of DIF-proven pemphigus and 30 non-pemphigus controls. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were analyzed for IgG4-IHC on lesional and perilesional biopsies to compare their diagnostic significance.

Statistical analysis: Data were analyzed using the Statistical Package for the Social Sciences version 29. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy of IgG4-IHC were calculated using standard formulae. Receiver operator curve analysis was performed for IgG4-IHC in lesional and perilesional skin to compare their diagnostic significance. The youden index was calculated using the formula "sensitivity + specificity – 1." $P < 0.05$ was considered statistically significant.

Results: Out of 30 cases enrolled for the study, 26 (86.6%) were diagnosed as pemphigus vulgaris and four (13.4%) as pemphigus foliaceous. The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of IgG4-IHC for pemphigus on lesional biopsy were 66.7%, 100%, 100%, 75%, and 83.3% while the sensitivity, specificity, PPV, NPV, and diagnostic accuracy for the perilesional biopsy were 56.7%, 100%, 69.8%, and 78.3%, respectively.

Conclusions: Our study indicated that IgG4-IHC is highly specific, but not sufficiently sensitive to replace DIF to diagnose pemphigus. IgG4-IHC on lesional skin is likely to be particularly valuable in a setting where a frozen section or immunofluorescence facility is not available. Further studies on larger samples are warranted to validate the role of IgG4-IHC in pemphigus.

Keywords: Immunoglobulin G4, Immunohistochemistry, Pemphigus

INTRODUCTION

Pemphigus comprises a group of immunoglobulin G (IgG)-mediated autoimmune vesiculobullous disorders of the skin and mucous membrane causing acantholysis or loss of cell adhesion leading to blister formation.[1] It is a relatively rare, but life-threatening disease, with a reported incidence ranging from 0.09 to 1.8% in India. With the increase in the incidence of other autoimmune disorders, the incidence of pemphigus is on the rise in India compared to European countries.[2]

There are different variants of pemphigus which differ in pathogenesis, severity, and blister location. Pemphigus vulgaris (PV) and pemphigus foliaceous (PF) are the two common forms of pemphigus. Both are characterized by IgG autoantibodies directed against desmoglein (Dsg), transmembrane glycoproteins of desmosomes which are primarily responsible for cell-to-cell adhesion between epithelial cells of skin and mucous membrane. PV occurs due to anti-Dsg3 autoantibodies and is characterized by flaccid blisters and erosions over skin and mucosa. PF is characterized by superficial bullae and erosions particularly over the sebaceous areas, occurring due to autoantibodies to Dsg-1 which are present over the superficial layers of the epidermis.[3] The binding of autoantibodies results in acantholysis and blistering. Patients with active disease have autoantibodies of both IgG1 and IgG4 subclasses, with IgG4 being predominant.[4]

At present, the diagnosis of pemphigus is made based on clinical presentation, histopathological examination (HPE) of the blister, and direct immunofluorescence (DIF) on normal-appearing perilesional skin. Indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA) can be done to detect autoantibodies in the serum of patients with active disease.[5,6] DIF plays a crucial role in diagnosing pemphigus, especially when the clinical presentation and histology are not characteristic. Tissue-bound autoantibodies are detected by DIF characterized by intercellular deposition of IgG, with or without complement deposition in the epidermis. DIF is considered the gold standard for the diagnosis of pemphigus due to its high sensitivity of 88–98%. [7,8]

Although of immense utility, the facility of DIF is limited as it requires a laboratory with infrastructure such as a frozen section, fluorescent-tagged antibodies, and a fluorescent microscope. DIF also warrants an additional tissue biopsy from the perilesional skin which may not be possible in cases with extensive involvement by disease, thus making diagnosis of pemphigus by DIF a challenging task.

The role of immunohistochemistry (IHC) in the diagnosis of pemphigus is currently being explored. As IHC for total IgG is not of diagnostic value due to high background staining, few studies have explored the possibility of using IgG4 in the diagnosis of pemphigus. [9-11] Comparison of immunoreaction of IgG4-IHC in the lesional and perilesional skin biopsies in cases of pemphigus has been studied very little in the literature. Hence, the present study aims to assess the utility of IgG4-IHC on formalin-fixed paraffin-embedded (FFPE) tissue in the diagnosis of pemphigus and to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of IgG4-IHC on lesional and perilesional skin, for diagnosis of pemphigus, considering DIF as the gold standard.

MATERIALS AND METHODS

This was a cross-sectional study, conducted on clinically diagnosed patients of pemphigus in the Department of Dermatology at Mahatma Gandhi Medical College and Research Institute, from June 2022 to May 2023. The Institutional Human Ethics Committee approval was obtained for the study (Ethical approval number: MGMCRI/IRC/04/2020/45/IHEC/183). Cases for which lesional biopsy and perilesional biopsies were sent to the Department of Pathology for HPE and DIF, respectively, and whose DIF were positive showing intercellular space deposits of IgG in the epidermis were included in the study.

A 3 mm punch biopsy was done under local anesthesia from the lesional skin (blister) and sent for routine HPE. After routine histopathology, IgG4-IHC was performed on the lesional skin.

Another 3 mm punch biopsy was sent from the peri-lesional skin (within 1 cm circumference of the lesion) in saline for DIF. Cases that showed linear deposits of IgG along intercellular space in the epidermis on DIF were included in the study. After DIF examination, the tissue was fixed in formalin overnight and routine histopathological tissue processing was done and paraffin-embedded blocks were used to prepare IgG4 IHC on the perilesional skin.

FFPE sections of both the lesional and peri-lesional skin were subject to IgG4 IHC using a standard protocol. Primary mouse monoclonal antibody for IgG4 (Biocare Medicals, USA) and secondary antibody Mach1 universal horseradish peroxidase, (Biocare Medicals, USA) were used. Distinct, continuous immunoreactivity of any intensity, localized to intercellular space was considered positive.

In the lesional biopsy, deposits over the roof or base of the blister or over both were considered positive. Cases with no reactivity or not meeting the criteria for positivity were considered negative.

Lesional and perilesional skin from 22 cases of bullous pemphigoid and eight cases of cutaneous vasculitis (n = 30) were used as negative controls for IgG4-IHC. Both cases and controls underwent the same protocol.

The methodology of the study is summarized in Figure 1.

The slides were blinded and evaluated independently by two pathologists for IgG4 IHC staining and a 100% interobserver agreement was achieved regarding positive and negative results for all cases.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences version 29. Descriptive data were represented by mean and standard deviation. Qualitative or categorical data were represented as frequencies and proportions.

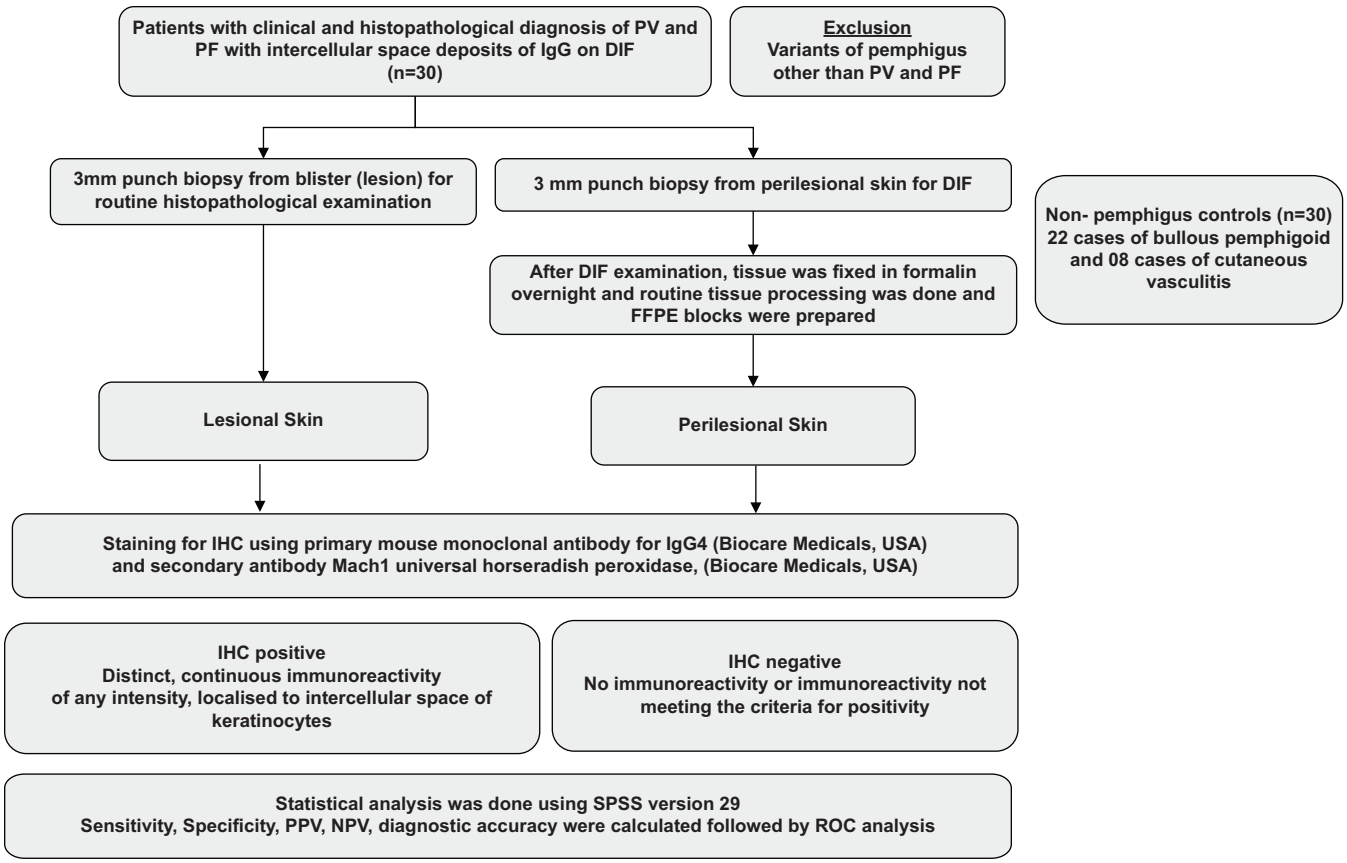

Figure 1: Schematic diagram representing methodology of the study. PV: Pemphigus vulgaris, PF: Pemphigus foliaceous, DIF: Direct immunofluorescence, IHC: Immunohistochemistry, FFPE: Formalin-fixed paraffin-embedded, PPV: Positive predictive value, NPV: Negative predictive value, ROC: Receiver operating curve.

Sensitivity, specificity, PPV, NPV, and diagnostic accuracy were calculated using standard formulae. The performance of IgG4-IHC was compared between lesional and perilesional skin in all cases of pemphigus. Receiver operator curve (ROC) analysis was performed for IgG4 in lesional and perilesional skin and the area under the curve (AUC) was calculated to compare their diagnostic significance. The Youden index was calculated using the formula "sensitivity + specificity – 1." $P < 0.05$ was considered statistically significant.

RESULTS

This was a 1-year cross-sectional study conducted on cases of pemphigus visiting Department of Dermatology at Mahatma Gandhi Medical College and Research Institute, from June 2022 to May 2023. During the 1-year study period, a total of 30 clinical, histopathological, and DIF proven cases of pemphigus were enrolled for the study. Of them, 26 (86.6%) were diagnosed as PV and 4 (13.4%) were PF.

Two cases of paraneoplastic pemphigus, one case of IgA pemphigus and pemphigus erythematosus each, encountered during the study period, were excluded from the study.

The age at presentation of pemphigus was found to range from 18 years to 79 years and the median age was 44.5 years. Of the 26 cases of pemphigus, 11 cases (42.3%) were between 41 and 50 years followed by seven cases (26.9%) between 31 and 40 years. Of the four cases of PF, 2 cases (50%) were in the age group of 21–30 years, and one case each in the age group of 31–40 years and 41–50 years.

Thirteen patients were male and 17 were female with a male-to-female ratio of 1:1.3. The male–to-female ratio for PV and PF were 1:1.6 and 1:0.3, respectively.

The duration of illness of pemphigus ranged from 15 days to 60 months with a mean duration of 7 months. More than 30% body surface area involvement was observed in 78.1% of the cases.

Details of histopathological and DIF findings of the cases are summarized in Tables 1 and 2, respectively.

Results of IHC for IgG4

The results of IgG4-IHC in the cases and negative controls are depicted in Tables 3 and 4.

Table 1: Histopathological profile of pemphigus.

Histopathological findings	PV (*n*=26) (%)	PF (*n*=4) (%)
Epidermal blister		
Subcorneal	0 (0)	4 (100)
Suprabasal	24 (92.4)	0 (0)
Intra-spinous	2 (7.6)	0 (0)
Acantholytic cells	26 (100)	3 (75)
Dermal inflammation	25 (89.3)	3 (75)
Eosinophils	4 (17.8)	1 (25)

PV: Pemphigus vulgaris, PF: Pemphigus foliaceous

Table 2: DIF findings of pemphigus cases.

DIF findings	PV (*n*=26) (%)	PF (*n*=4) (%)
Site of antibody deposition		
Upper epidermis	0 (0)	4 (100)
Lower epidermis	1 (3.8)	0 (0)
Full-thickness epidermis	25 (96.2)	0 (0)
Type of antibody		
IgG	15 (57.7)	2 (50)
IgG+C3	11 (42.3)	2 (50)

IgG: Immunoglobulin G, PV: Pemphigus vulgaris, PF: Pemphigus foliaceous, DIF: Direct immunofluorescence

Table 3: IgG4-IHC findings in the lesional skin biopsies of cases and controls.

Diagnosis on DIF	IgG4-IHC-positive	IgG4-IHC-negative
PV (*n*=26)	17	09
PF (*n*=04)	03	01
Pemphigus (PV and PF)	20	10
Non-pemphigus controls (*n*=30)	0	30

IgG4: Immunoglobulin G4, IHC: Immunohistochemistry, PV: Pemphigus vulgaris, PF: Pemphigus foliaceous, DIF: Direct immunofluorescence

In the lesional skin, out of 26 cases of PV, 17 (65.3%) showed immunoreactivity for IgG4 and among four cases of PF, 3 cases (75%) showed immunoreactivity for IgG4. The sensitivity of IgG4 for PV was 86.6% and the sensitivity of IgG4 for PF was 75% in the lesional skin. The overall sensitivity of IgG4 for pemphigus in the lesional skin was 66.6%.

In the perilesional skin, only 14 (53.8%) out of 26 cases of PV were positive for IgG4 and 3 (75%) of out of four cases of PF was immunoreactive for IgG4. The sensitivity of IgG4 for PV was 53.8% and the sensitivity of IgG4 for PF was 75% in the perilesional skin. The overall sensitivity of IgG4 for pemphigus in the perilesional skin was 56.6%.

The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of IgG4 for both PV and PF in the lesional and perilesional skin are depicted in Table 5.

Table 4: IgG4-IHC findings in the perilesional skin biopsies of cases and controls.

Diagnosis on DIF	IgG4-positive	IgG4-negative
PV (*n*=26)	14	12
PF (*n*=04)	03	01
Pemphigus (PV and PF)	17	13
Non-pemphigus controls (*n*=30)	0	30

IgG4: Immunoglobulin G4, IHC: Immunohistochemistry, PV: Pemphigus vulgaris, PF: Pemphigus foliaceous, DIF: Direct immunofluorescence

The clinical, histopathological, DIF, and IgG4-IHC findings in PV and PF are showed in Figures 2 and 3, respectively.

ROC analysis

The AUC achieved statistical significance for utility of IgG4-IHC on lesional skin (P = 0.000, i.e., <0.001) as well as in the perilesional skin (P = 0.000, i.e., <0.001) in diagnosing pemphigus. On comparison of analysis of ROC of IgG4 in lesional and perilesional skin, the difference in AUC was 0.05 (0.833–0.783) (P < 0.001) [Figure 4].

DISCUSSION

During the 1-year study period, a total of 30 clinical, histopathological, and DIF proven cases of pemphigus were enrolled for the study. Of them, 26 (86.6%) were diagnosed as PV and 4 (13.4%) were PF. The median age at presentation of pemphigus in the present study was 44.5 years. This is in concordance with the age at presentation in India which is 37 years in females and 58 years in males. In a study by Kridin and Schmidt on the epidemiology of pemphigus across many countries in the world, most patients of pemphigus were aged between 45 and 65 years at presentation.[12,13]

There was female preponderance of pemphigus in the present study. This is in in concordance with most other studies across the globe and in India where the male-to-female ratio ranged from 1:1.2 to 1:5. [12,13]

Duration of illness at presentation was 15 days–60 months while in study in Eastern India the duration ranged from 0.16 to 108 months. Chowdhury *et al.* reported 68.3% cases with more than 30% body surface area which is lower than that in the present study, where it was 78.1% cases. On histopathology, 96.6% cases showed acantholytic cells and 93.3% showed dermal inflammation which is in concordance to previous studies. DIF study from perilesional biopsy showed IgG and C3 deposits in 56.6% cases and 43.3% showed only IgG deposits.[14]

Abreu Velez *et al.* reported around 98% correlation between IHC and DIF in various autoimmune bullous disorders while

Table 5: Diagnostic utility of IgG4-IHC in the lesional and perilesional skin biopsies in the diagnosis of pemphigus.

IgG4	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)	Youden index	Area under ROC curve	*P*-value
Lesional skin								
Pemphigus (PV+PF)	66.7 (47–83)	100 (88–100)	100 (83–100)	75.0 (64–83)	83.3 (72–92)	0.333	0.833	0.000 (<0.001)
Perilesional skin								
Pemphigus (PV+PF)	56.7 (37–75)	100 (88–100)	100 (81–100)	69.8 (61–78)	78.3 (66–88)	0.433	0.783	0.000 (<0.001)

IgG4: Immunoglobulin G4, IHC: Immunohistochemistry, PPV: Positive predictive value, NPV: Negative predictive value, ROC: Receiver operator curve, PV: Pemphigus vulgaris, PF: Pemphigus foliaceous

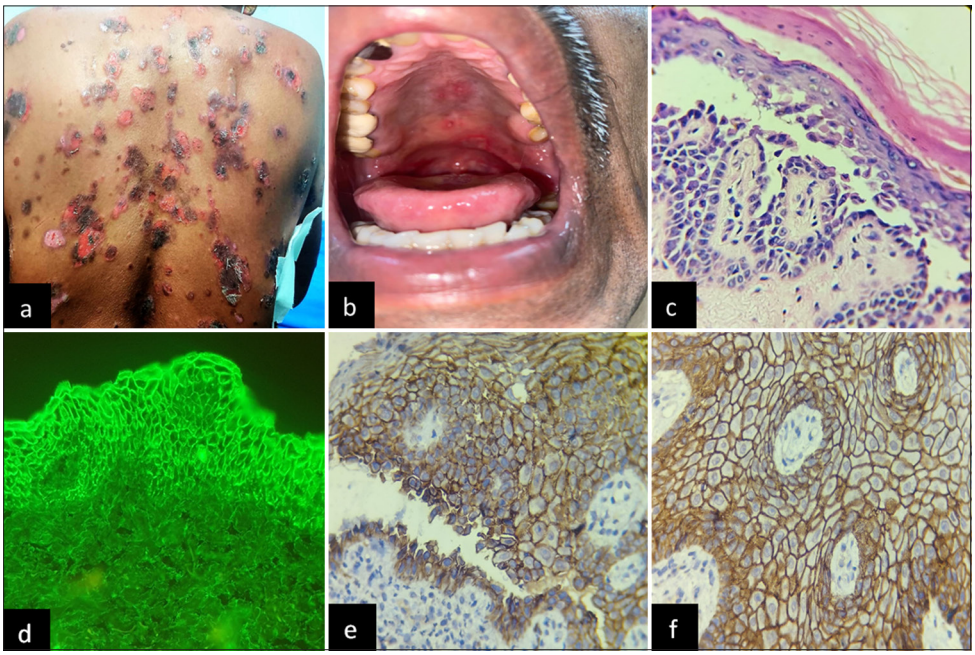

Figure 2: Clinical, histopathological, direct immunofluorescence (DIF), and Immunoglobulin G4 (IgG4)-Immunohistochemistry (IHC) of pemphigus vulgaris. (a) Multiple flaccid bullae and erosions over trunk. (b) Mucosal lesions over hard palate. (c) Photomicrograph showing suprabasal blister with acantholytic cells and "row of tombstone" appearance of basal cells (hematoxylin and eosin ×40). (d) Intercellular space positivity of IgG (DIF ×10). (e) IHC staining on lesional skin showing intercellular space expression of IgG4 over roof and floor of the blister (IHC ×40). (f) IHC staining on perilesional skin showing intercellular space positivity of IgG4, pattern similar to DIF (IHC ×40).

Glauser *et al*. reported lower sensitivity and specificity of IHC when compared to DIF in cases of bullous pemphigoid. [15,16]

In the present study, the overall sensitivity of IgG4 for pemphigus in the lesional biopsy was 66.6%. The sensitivity of IgG4 for pemphigus in the perilesional biopsy was 56.6%. The sensitivity of IgG4-IHC in lesional and perilesional skin is lower in the present study compared to similar study by Zhang *et al.* conducted on 12 cases of PV and six cases of PF on comparison with IIF results. The sensitivity of IgG4 IHC was 75.0% for PV and 66.7% for PF with an overall sensitivity of 72.2%. The specificity was 97.2% with one case of bullous pemphigoid which showed false positivity.[9] In the present, the specificity was 100% in both lesional and perilesional skin of PV and PF.

In the same study, the sensitivity was 80.0% for PV and 100.0% for PF in lesions with acantholysis and the overall sensitivity of IgG4 for pemphigus in acantholytic lesions was 85.7%.[9] This shows that the sensitivity was higher in the lesional skin (skin with acantholysis) compared to those without lesions which are similar to the findings of our study where the lesional skin showed higher sensitivity compared to the perilesional skin.

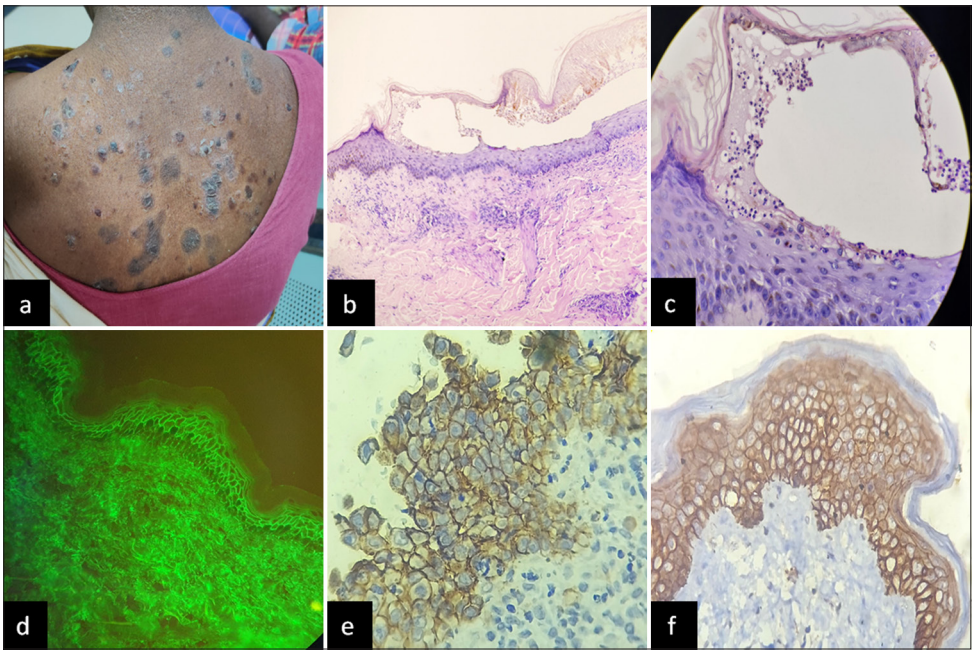

Figure 3: Clinical, histopathological, direct immunofluorescence (DIF), and Immunoglobulin G4 (IgG4) Immunohistochemistry (IHC) of pemphigus foliaceous. (a) Superficial erosions over trunk. (b) Photomicrographs showing subcorneal blister with mild inflammation (hematoxylin and eosin [H&E] ×4). (c) High-power view of the subcorneal blister (H&E ×40). (d) Intercellular space positivity of IgG (DIF ×10). (e) Immunohistochemical staining on perilesional skin showing intercellular space expression of IgG4 along the floor (IHC ×40). (f) Immunohistochemical staining on perilesional skin showing intercellular space positivity of IgG4, pattern similar to DIF (IHC ×40).

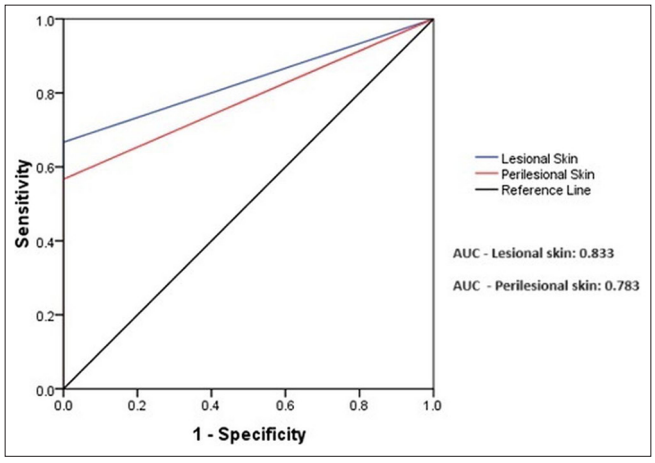

Figure 4: Comparison of receiver operating curve curves of immunoglobulin G4 in lesional and perilesional skin in pemphigus. AUC: Area under curve.

Heidarpour *et al.* compared IgG4 IHC with IIF on 29 cases of PV and six cases of PF. The sensitivity and specificity of PV and PF on lesional skin in the study was 72.4% and 83.3% with an overall sensitivity and specificity for pemphigus of 74.2% and 82.8%, respectively.[10]

Al-Shenawy performed IgG4 and C3d on 30 cases of PV and 10 cases of PF with 37 controls. The overall sensitivity of IgG4 for pemphigus was 93.3%. The PPV and NPV were 81.2% and 76.3%, respectively.[17]

García-Lechuga *et al.* performed IgG4-IHC on four cases of pemphigus and IgG4 was positive in all four cases with a sensitivity of 100%.[11]

Rana *et al.* conducted a similar study on 20 cases of PV and four cases of PF with a sensitivity of 80% for PV and 75% for PF. The overall sensitivity of IgG4-IHC for pemphigus was 73%.[18]

The specificity in the present study is high; however, the sensitivity is low compared to the previous studies where the sensitivity ranged from 74% to 93%. On comparison of sensitivity of lesional and perilesional skin, the sensitivity is high in lesional group compared to the perilesional group which is concordant with the previous studies [9,10,18]

As IgG4 is predominant during the active phase of the disease, the sensitivity significantly increases in the presence of blister. The low sensitivity of IgG4 over perilesional biopsy than the lesional biopsy with acantholysis is also explained by the high IgG4 immunoreactivity in the acantholytic blister. [9,19]

The AUC achieved statistical significance for utility of IgG4-IHC on lesional skin in diagnosing pemphigus while it was not significant in the diagnosis of pemphigus in the perilesional skin.

Though, studies have concluded that IgG4 IHC was a sensitive and specific test, the present study shows that IgG4-IHC is not sufficiently sensitive to replace DIF to confirm the diagnosis of pemphigus.

Further studies correlating with circulating autoantibodies by IIF or ELISA would help in assessing the reasons for low sensitivity of the test.

Limitations

Further studies with a larger sample and additional complement markers are warranted to validate the diagnostic efficacy of this test. Correlation between circulating autoantibodies detected by IIF or ELISA and IHC would help to understand the influence of activity of the disease in determining the test results.

CONCLUSIONS

IgG4-IHC is not sufficiently sensitive to replace DIF to confirm the diagnosis of pemphigus. However, it is a highly specific test and is less expensive compared to DIF. IgG4-IHC on lesional skin would be valuable in a setting where fresh-frozen tissue or immunofluorescence facility is not available, especially in patients with active blister.

It would also be valuable in a scenario where perilesional skin for DIF was not sent, as there was no clinical suspicion of pemphigus. In such cases, IgG4-IHC on formalin-fixed lesional skin biopsy would give a confirmative diagnosis thereby alleviating the need for an additional fresh unfixed biopsy from perilesional skin.

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Authors' contributions

SB and BK: Conceptualization, drafting of manuscript; SB: Data curation; SB, BK, SS: Critical and intellectual evaluation; All authors approved the final manuscript.

Ethical approval: The research/study was approved by the Institutional Review Board at Mahatma Gandhi Medical College and Research Institute, number MGMCRI/IRC/04/2020/45/IHEC/183, dated August 17, 2020.
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