ARUP LABORATORIES
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Jonathan R. Genzen, MD, PhD, Chief Medical Officer

Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/31/1993
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Basement Membrane Zone and Cell Surface (Epithelial) Antibodies, IgG and IgA by IIF

ARUP test code 0090299

EER Epithelial Skin Antibodies

See Note

Authorized individuals can access the ARUP Enhanced Report using the following link:

[redacted]

Epithelial Skin Antibodies

See Note

CLINICAL INFORMATION
Blisters, erosions, fine scaly patches on skin. Presumptive diagnosis is immunobullous disease, possible pemphigus or pemphigoid.

Specimen Details
[redacted] - ; Collected: 11/3/2023; Received: 11/6/2023

DIAGNOSTIC INTERPRETATION

Consistent with IgG-variant pemphigus without evidence for pemphigoid

(See Results and Comments including further testing recommendations)

RESULTS
Indirect Immunofluorescence (IIF)

Cell Surface (CS)/Intercellular Substance (ICS) IgG, IgG4, and IgA Antibodies

IgG: Positive, titer 1:640 (H), monkey esophagus substrate
Positive, titer 1:160 (H), intact human skin substrate

IgG4: Positive, titer greater than 1:40 (H), monkey esophagus substrate
Positive, titer 1:40 (H), intact human skin substrate

IgA: Negative, monkey esophagus substrate
Negative, intact human skin substrate

Reference Range:
Negative - Titer less than 1:10
Borderline - Titer 1:10

H=High, L=Low, *=Abnormal, C=Critical

Positive (H) - Titer greater than 1:10

(H) = high/positive

Basement Membrane Zone (BMZ) IgG, IgG4, and IgA Antibodies

IgG: Negative, monkey esophagus substrate
Negative, human split skin substrate

IgG4: Negative, monkey esophagus substrate
Negative, human split skin substrate

IgA: Negative, monkey esophagus substrate
Negative, human split skin substrate

Reference Range:
Negative - Titer less than 1:10
Borderline - Titer 1:10
Positive (H) - Titer greater than 1:10

Localization Pattern on Human BMZ Split Skin:
Epidermal (roof) or combined epidermal-dermal (roof and floor) IgG and/or IgG4 BMZ antibodies = pemphigoid (including pemphigoid gestationis, bullous pemphigoid, some types of mucous membrane pemphigoid)

Dermal (floor) IgG and/or IgG4 BMZ antibodies = epidermolysis bullosa acquisita or bullous lupus erythematosus or anti-laminin-332 pemphigoid or anti-p200 (laminin gamma-1) pemphigoid or another rare pemphigoid subtype

Epidermal (roof), combined epidermal-dermal (roof and floor), or, dermal (floor) IgA BMZ antibodies = linear IgA disease (including linear IgA bullous dermatosis and chronic bullous disease of childhood)

IgA and IgG basement membrane zone antibodies may be co-expressed in basement membrane zone antibody-associated diseases

(H) = high/positive

COMMENTS

Specific

The indirect immunofluorescence findings, demonstrating positive IgG, including IgG4, cell surface (CS), also known as intercellular substance (ICS), antibodies on both monkey esophagus substrate and intact human skin substrate, support the diagnosis of pemphigus vulgaris or pemphigus foliaceus or another IgG pemphigus variant. Pemphigus foliaceus and pemphigus vulgaris can be distinguished by the predominance of IgG desmoglein 1 or IgG desmoglein 3 antibodies, respectively, determined by enzyme-linked immunosorbent assay (ELISA). ELISA testing for IgG desmoglein 1 and IgG desmoglein 3 antibodies is highly sensitive, with greater than 90 percent of patients with pemphigus showing increased levels of one or both antibodies. Correlation with ELISA testing for IgG desmoglein 1 and IgG desmoglein 3 antibody levels is recommended. The additional testing can be accomplished on this serum specimen by contacting ARUP Client Services, 1-800-242-2787, option 2, with add-on test request for:
- Desmoglein 1 and Desmoglein 3 (Pemphigus) Antibodies, IgG by ELISAs (ARUP test number 0090649).

IgG CS/ICS antibody titers by indirect immunofluorescence and IgG desmoglein antibody levels by ELISA correlate with disease

activity in pemphigus foliaceus and pemphigus vulgaris. Of note, cell surface reactivity by indirect immunofluorescence can be observed transiently and/or nonspecifically in normal individuals, and in patients with infections, drug reactions, and other mucocutaneous disorders.

The negative indirect immunofluorescence findings for IgG, including IgG4, and IgA basement membrane zone antibodies with monkey esophagus and human split skin substrates, also known as salt split skin, do not provide support for, but do not rule out, the diagnoses of concurrent pemphigoid, epidermolysis bullosa acquisita, and linear IgA disease or a mixed epithelial antibody profile. The results do not rule out mucous membrane/cicatricial pemphigoid because most patients with this pemphigoid variant do not have positive/increased basement membrane zone antibodies detected.

IgG BP180 and/or IgG BP230 antibody levels, determined by ELISAs, may be more sensitive diagnostic markers than indirect immunofluorescence in pemphigoid, and the IgG type VII collagen antibody level, determined by ELISA, may be a more sensitive diagnostic marker than indirect immunofluorescence in epidermolysis bullosa acquisita. If clinically indicated to further evaluate for concurrent pemphigoid and/or epidermolysis bullosa acquisita and/or mixed epithelial antibody expression, additional testing can be accomplished on this serum specimen by contacting ARUP Client Services, 1-800-242-2787, option 2, with add-on test request(s) for:
- Bullous Pemphigoid (BP180 and BP230) Antibodies, IgG by ELISAs (ARUP test number 0092566) and/or
- Collagen Type VII Antibody, IgG by ELISA (ARUP test number 2010905).

Clinical correlation is needed, including with direct immunofluorescence findings on a biopsy specimen and treatment status, with consideration for additional recommended ELISA testing, particularly for IgG desmoglein 1 and IgG desmoglein 3 antibodies, and for monitoring antibody profiles by indirect immunofluorescence and antibody levels by ELISAs in assessing disease expression and activity, including response to therapy.

If it would be helpful to discuss the patient case with this report, contact ARUP Client Services at 1-800-242-2787, option 2, and ask to speak with the Immunodermatology Laboratory at the University of Utah regarding patient results.

General

More than 80 percent of patients with pemphigus have positive epithelial cell surface (CS) antibodies, also known as intercellular substance (ICS) antibodies, in their sera identified by indirect immunofluorescence. IgG4 subclass reactivity by indirect immunofluorescence may be more sensitive than IgG in some patients with pemphigus. Serum antibody titers correlate with disease activity, and CS/ICS antibodies may be in low titer or negative in patients whose disease activity is minimal and/or under therapeutic control. CS/ICS antibodies are implicated in the pathophysiology of pemphigus. CS/ICS antibodies are typically not detected in normal individuals or in patients with other immunobullous diseases, although cell surface reactivity may be observed transiently and/or nonspecifically in normal individuals and in patients with drug reactions, infections, and other mucocutaneous diseases. IgG CS/ICS antibodies characteristically are positive by indirect immunofluorescence in IgG pemphigus variants, including pemphigus foliaceus and pemphigus vulgaris. IgA CS/ICS antibodies are positive by indirect immunofluorescence in patients with IgA pemphigus and in some pemphigus variants along with positive IgG CS/ICS antibodies. Approximately 40 percent of patients with nonclassical IgG/IgA pemphigus have an underlying systemic disease when diagnosed, malignancy being the most

common.

Approximately 80 percent of patients with bullous pemphigoid, epidermolysis bullosa acquisita, and linear IgA bullous dermatosis have positive antibodies to basement membrane zone components in their sera detected by indirect immunofluorescence. Approximately 50 percent of patients with mucous membrane/cicatricial pemphigoid demonstrate antibodies to basement membrane zone components detected by indirect immunofluorescence. IgG4 subclass reactivity by indirect immunofluorescence may be more sensitive than IgG in some patients with pemphigoid and epidermolysis bullosa acquisita. The immunoglobulin class of basement membrane zone antibodies and pattern of antibody localization on split skin substrate distinguish the diseases. Positive serum IgA epithelial basement membrane zone antibodies are highly specific diagnostic markers for linear IgA disease. IgA basement membrane zone antibodies by indirect immunofluorescence may be found in variant presentations of mucous membrane pemphigoid and epidermolysis bullosa acquisita. Moreover, IgA basement membrane zone antibodies may be co-expressed with IgG basement membrane zone antibodies in some patients with pemphigoid, including mucous membrane/cicatricial pemphigoid, and in linear IgA/IgG bullous dermatosis.

Basement membrane zone and cell surface/intercellular substance antibodies characteristically develop together in paraneoplastic pemphigus. Mixed antibody profiles, generally, may be found: in concurrent disease presentations with co-dominant autoantibody expression; as incidental cross-over antibodies with dominant features of one immunobullous disease; in autoimmune diseases in patients who are multiple autoantibody producers; in drug reactions; as a spurious result from interference in an assay; as nonspecific expression of one or more of the antibodies; as well as associated with paraneoplastic conditions/malignancy including paraneoplastic pemphigus and others.

TESTING METHODS
Indirect Immunofluorescence (IIF)

IgG, IgG4, and IgA Cell Surface (CS)/Intercellular Substance (ICS) and Epithelial Basement Membrane Zone (BMZ) Antibodies

Patient serum is progressively diluted beginning at 1:5 in four two-fold screening dilutions, layered on sections of human skin split at the basement membrane zone, intact human skin, and monkey esophagus substrates, and reacted with fluorescein isothiocyanate (FITC)-conjugated antibodies to IgG and IgA. When positive, the serum is further diluted in two-fold reductions to the limiting dilution of antibody detection or to a maximum dilution of 1:40,960. The limiting-dilution, end-point titer is reported for each substrate, and the pattern of staining on split skin substrate also is reported. FITC-conjugated anti-IgG4 is tested to increase test sensitivity (maximum serum dilution of 1:40). This indirect immunofluorescence testing was developed and its performance characteristics determined by the Immunodermatology Laboratory at the University of Utah. It has not been cleared or approved by the FDA (US Food and Drug Administration). FDA clearance or approval currently is not required for this testing performed in a CLIA-certified laboratory (Clinical Laboratory Improvement Amendments) and intended for clinical use. [Indirect immunofluorescence, three antibodies on three substrates (IIF X 9) with two limiting dilution, end-point titers (antibody titer X 2)]

Electronically signed by [redacted] on 11/15/23 at 9:55 PM.
Performed At: IMMUNODERMATOLOGY LABORATORY
417 S. WAKARA WAY, SUITE 2151
SALT LAKE CITY, UT 84108
Medical Director: KRISTIN M. LEIFERMAN, MD

H=High, L=Low, *=Abnormal, C=Critical

CLIA Number: 46D0681916

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
EER Epithelial Skin Antibodies	23-307-104145	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Epithelial Skin Antibodies	23-307-104145	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical