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Review Article

Clinical usefulness of serum antibodies as biomarkers of gastrointestinal and liver diseases

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ABSTRACT

The progressively growing knowledge of the pathophysiology of a number of immune-mediated gastrointestinal and liver disorders, including autoimmune atrophic gastritis, coeliac disease, autoimmune enteropathy, inflammatory bowel disease, autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis and autoimmune pancreatitis, together with the improvement of their detection methods have increased the diagnostic power of serum antibodies. In some cases – coeliac disease and autoimmune atrophic gastritis – they have radically changed gastroenterologists' diagnostic ability, while in others – autoimmune hepatitis, inflammatory bowel disease and autoimmune pancreatitis – their diagnostic performance is still inadequate. Of note, serum antibody misuse in clinical practice has raised a number of controversies, which may generate confusion in the diagnostic management of the aforementioned disorders. In this review, we critically re-evaluate the usefulness of serum antibodies as biomarkers of immune-mediated gastrointestinal and liver disorders, and discuss their pitfalls and merits.

1. Introduction

The expansion of the pathogenic knowledge of immune-mediated gastrointestinal and liver diseases, including autoimmune atrophic gastritis (AAG), coeliac disease (CoeD), inflammatory bowel disease (IBD), autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC) and autoimmune pancreatitis (AIP), has led to a deeper awareness of the clinical management of these conditions [1–4]. In particular, serum antibodies have increased our diagnostic power in most of the aforementioned disorders (Tables 1 and 2), although their misuse has often led to diagnostic mistakes thus generating a number of controversies regarding their accuracy and appropriate use in real life. Fig. 1 shows the accuracy of serum antibodies according to the figures commonly reported in the literature.

On this basis, we aimed to critically re-evaluate the usefulness of serum antibodies as biomarkers in immune-mediated gastrointestinal and liver disorders, and to discuss both their pitfalls and merits. For clarity, we decided to divide the review and discussion by diseases instead of by biomarkers, even if serum antibodies are the core of the review.

2. Autoimmune atrophic gastritis

AAG is an organ-specific disease which affects the corpus-fundus mucosa of the stomach, causing hypo-achlorhydria, deficiency of vitamin B_{12} and iron [5,6], and may predispose to gastric adenocarcinoma or type I neuroendocrine tumour [7,8]. Specific clinical symptoms may be absent for many years [9], and anti-parietal cell antibodies (PCA) and anti-intrinsic factor antibodies (IFA) could be potentially helpful in the diagnosis of this condition (Table 1) [10,11].

PCA are directed against the α and β subunit of gastric H^+/K^+ adenosine triphosphatase [12–14], and they can be identified by either immunofluorescence or enzyme-linked immunosorbent assay (ELISA), the latter being more accurate than the former [15,16]. How to interpret serum PCA positivity in the absence of gastric atrophy is still under debate [17–19]. We recently followed-up 58 patients with serum PCA positivity and normal gastric mucosa, and we observed that thirteen of them subsequently developed atrophy over a median 30-month follow-up period [20]. Of course, further studies are needed to verify whether the isolated PCA pos-

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Table 1
Serum antibody biomarkers of immune-mediated gastrointestinal disorders.

Antibody	Acronym	Disease	Target	Detection method
Anti-gastric parietal cell	PCA	Autoimmune atrophic gastritis	H+/K+ ATPase	ELISA
Anti-intrinsic factor	IFA		Intrinsic factor	ELISA, IB
Anti-tissue transglutaminase IgA	TTA	Coeliac disease	Tissue transglutaminase	ELISA, CLIA
Anti-endomysial IgA	EMA		Tissue transglutaminase	IF
Anti-deamidated gliadin peptide IgA	DGP		Deamidated gliadin-related peptide	ELISA
Anti-enterocyte	EA	Autoimmune enteropathy	Enterocyte	IF
Anti-*Saccharomyces cerevisiae*	ASCA	Crohn's disease	Yeast mannan	IF, ELISA
Perinuclear anti-neutrophil cytoplasmic	pANCA	Ulcerative colitis	Neutrophil cytoplasm	IF

Abbreviations: CLIA, chemiluminescence immunoassay; ELISA, enzyme linked immunosorbent assay; IB, immunoblot immunoassay; IF, immunofluorescence; Ig, immunoglobulin; tRNA, transfer ribonucleic acid; UGA, uracil–guanine–adenine.

Table 2
Serum antibody biomarkers of immune-mediated liver disorders.

Antibody	Acronym	Disease	Target	Detection method
Anti-nuclear	ANA	Autoimmune hepatitis	Heterogeneous	IF
Anti-smooth muscle	SMA		Filamentous actin	IF
Anti-liver kidney microsomal	LKM		Cytochrome P450	IF
Anti-soluble liver antigen/liver-pancreas	SLA/LP		UGA serine tRNA-associated protein complex	ELISA
Anti-liver cytosol 1	LC1		Formimino-transferase cyclodeaminase (FTCD)	IF
Perinuclear anti-neutrophil cytoplasmic	pANCA	Primary sclerosing cholangitis	Neutrophil cytoplasm	IF
Anti-mitochondrial	AMA	Primary biliary cholangitis	Mitochondria	IF
Immunoglobulin G4	IgG4	Autoimmune pancreatitis	Pleiotropic	Nephelometry

Abbreviations: ELISA, enzyme linked immunosorbent assay; IF, immunofluorescence; Ig, immunoglobulin; tRNA, transfer ribonucleic acid; UGA,uracil–guanine–adenine.

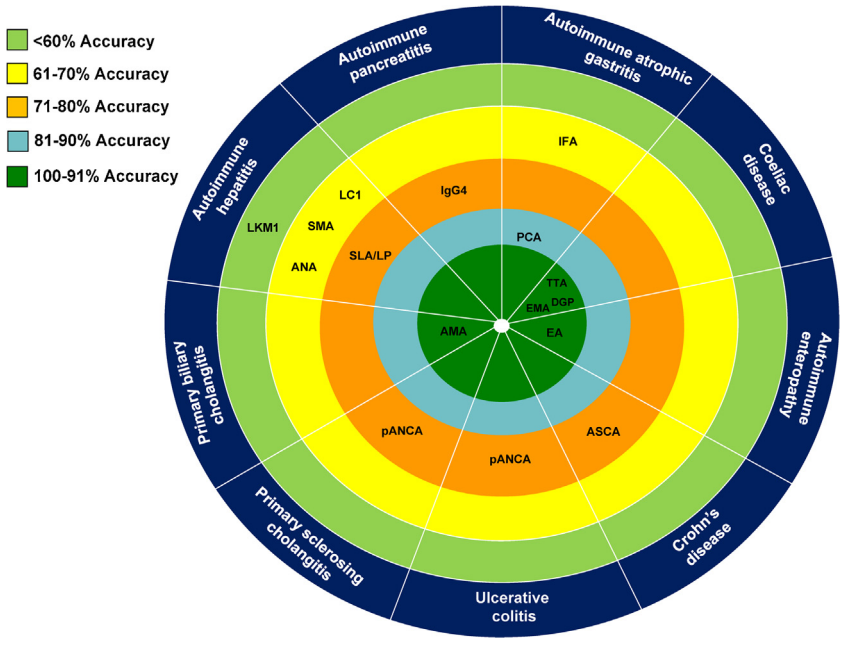

Fig. 1. Schematic representation of the accuracy of the most commonly used serum antibodies in the diagnosis of immune-mediated gastrointestinal and liver diseases. Accuracy is calculated as the average of sensitivity and specificity by using the best available tests in the literature. AEA, anti-enterocyte antibody; AGA, anti-gliadin antibody; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; ASCA, anti-*Saccharomyces cerevisiae* antibody; DGP, anti-deamidated gliadin peptide antibody; EMA, anti-endomysial antibody; GCA, anti-goblet cell antibody; IFA, anti-intrinsic factor antibody; Ig, immunoglobulin; LC1, anti-liver cytosol 1 antibody; LKM1, anti-liver kidney microsomal antibody 1; pANCA, perinuclear anti-neutrophil cytoplasmic antibody; PCA, anti-gastric parietal cell antibody; SLA/LP, anti-soluble liver antigen/liver-pancreas antibody; TTA, anti-tissue transglutaminase antibody.