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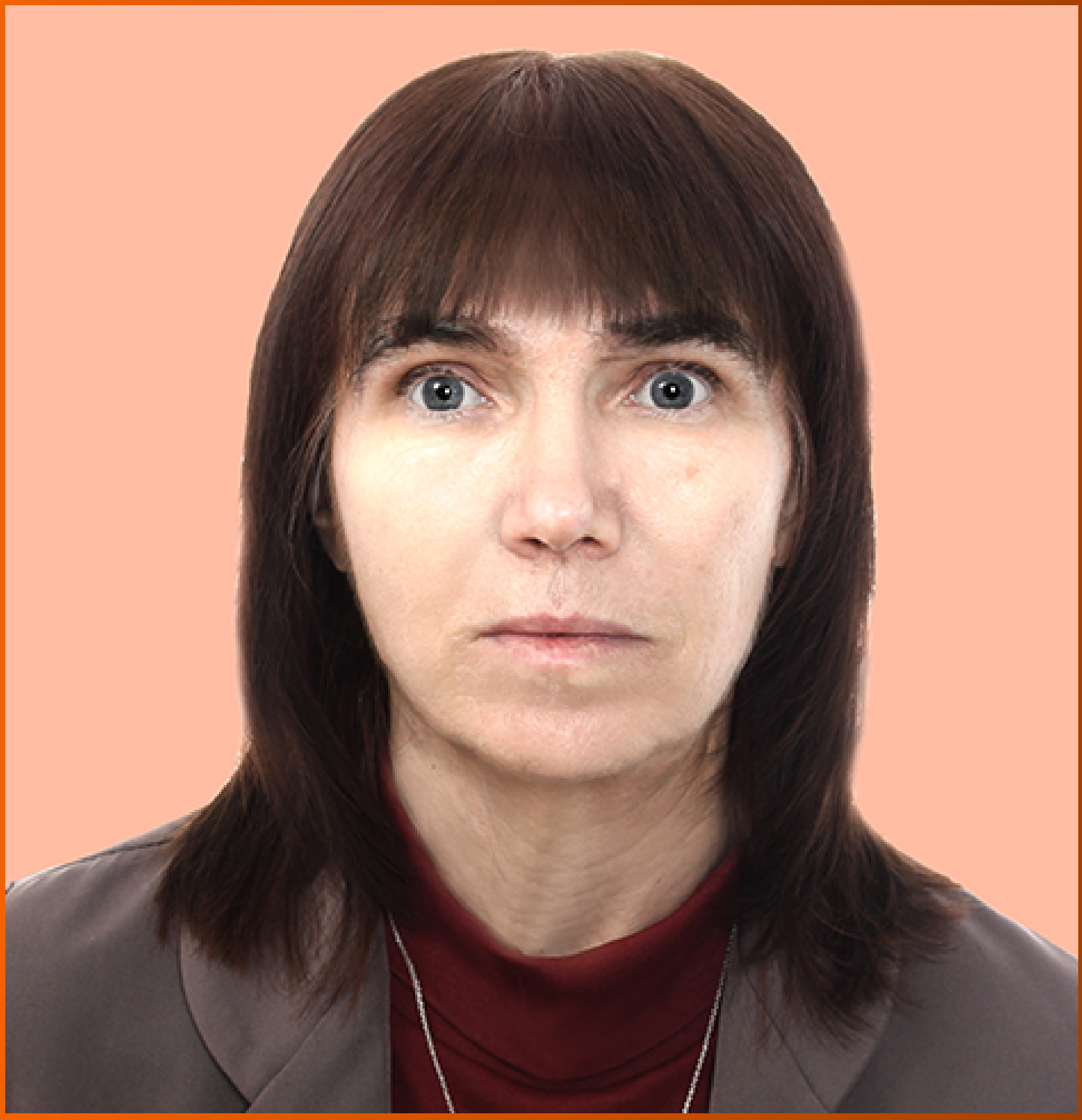

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Contents

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Contents

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Contents

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MINIREVIEWS

Serum biomarkers for the differentiation of autoimmune pancreatitis from pancreatic ductal adenocarcinoma

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Abstract

Autoimmune pancreatitis (AIP), a chronic inflammation caused by the immune system attacking the pancreas, usually presents imaging and clinical features that overlap with those of pancreatic ductal adenocarcinoma (PDAC). Serum biomarkers, substances that quantitatively change in sera during disease development, are a promising non-invasive tool with high utility for differentiating between these diseases. In this way, the presence of AIP is currently suspected when serum concentrations of immunoglobulin G4 (IgG4) antibody are elevated. However, this approach has some drawbacks. Notably, IgG4 antibody concentrations are also elevated in sera from some patients with PDAC. This review focuses on the most recent and relevant serum biomarkers proposed to differentiate between AIP and PDAC, evaluating the usefulness of immunoglobulins, autoantibodies, chemokines, and cytokines. The proposed serum biomarkers have proven useful, although most studies had a small sample size, did not examine their presence in patients with PDAC, or did not test them in humans. In addition, current evidence suggests that a single serum biomarker is unlikely to accurately differentiate these diseases and that a set of biomarkers will be needed to achieve adequate specificity and sensitivity, either alone or in

combination with clinical data and/or radiological images.

Key Words: Autoimmune pancreatitis; Pancreatic ductal adenocarcinoma; Serum; Biomarkers; Differentiation

Core Tip: The imaging and clinical features of autoimmune pancreatitis commonly overlap with those of pancreatic ductal adenocarcinoma. This study reviews the most recent and relevant serum biomarkers proposed to differentiate between these diseases of the pancreas, including serum immunoglobulins, autoantibodies, chemokines, and cytokines, evaluating their usefulness for this purpose. One of the key conclusions is that a panel of various serum biomarkers appears to be necessary for an accurate differentiation between these diseases, either alone or in combination with clinical data and/or radiological images. Importantly, further research is warranted to assess the usefulness of these promising serum biomarkers in clinical practice

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INTRODUCTION

Autoimmune pancreatitis (AIP) is a rare entity that represents 2%-10% of chronic pancreatitis (CP) cases [1]. Elevated serum concentrations of immunoglobulin (Ig), especially IgG4, have been observed in the majority of AIP patients[2], and Umehara *et al*[3] introduced the concept of IgG4-related disease in 2011, including AIP as one of these disorders. AIP can be classified into types 1 and 2, with more than 90% of cases corresponding to type 1[4]. Type 1 is associated with high serum IgG4 concentrations, unlike type 2[5]. Given the large proportion of cases that are type 1, type 1 AIP is referred to as AIP in this review.

The clinical and radiological characteristics of AIP can mimic those of pancreatic ductal adenocarcinoma (PDAC), leading to misdiagnosis and therapeutic errors that increase the morbidity and mortality of patients. This difficulty in differentiating AIP from PDAC has been well documented, with up to 15% of neoplasms being classified as AIP and up to 36% of AIP cases diagnosed as cancer. It should also be borne in mind that AIP, like other forms of CP, increases the risk of PDAC and therefore requires close follow-up[6]. The similarity between AIP and PDAC means that invasive methods must be applied, when possible, to establish the differential diagnosis using histological criteria.

The current diagnostic criteria for AIP, displayed in Table 1, were established in 2011 by consensus among international experts[7], who recognized that AIP has two different histopathological and clinical subtypes, types 1 and 2, as noted above.

Although serum IgG4 antibodies are used for the diagnosis of AIP, elevated IgG4 concentrations are not AIP-specific and are observed in other diseases, including PDAC[8]. In a study of 510 patients, Ghazale *et al*[9] observed increased serum IgG4 in around 10 % of PDAC cases, yielding false positives. In addition, not all patients with AIP have elevated serum IgG4 Levels, resulting in false negatives and an inadequate diagnostic accuracy[10]. Hence, this serological biomarker alone does not define the disease, and its usefulness is more limited in type 2 AIP.

Radiological criteria should also not be used alone, because they can lead to an erroneous differential diagnosis between AIP and PDAC[11]. Current recommendations require an exhaustive study to establish the diagnosis, including histological and morphological criteria and the response of patients to corticosteroid treatment[8]. Although not included in recommendations, clinical characteristics can also help the differential diagnosis of PDAC and the two AIP subtypes. Weight loss and anorexia are more frequently observed in PDAC, while other organs are more commonly involved in AIP[12]. Ultrasound endoscopy plays a key role in the diagnosis, allowing the morphology to be assessed and a core needle biopsy to be obtained before the proposal of a percutaneous biopsy or videolaparoscopy[13].

Hence, new serological biomarkers other than IgG4 antibodies are needed for the differential diagnosis in order to rule out malignancy and establish the appropriate treatment, avoiding unnecessary surgical resection and the erroneous treatment of patients. Some authors have increased the diagnostic potential of IgG4 by combining it with other serum biomarkers. Chang *et al*[14] increased the diagnostic accuracy to differentiate between AIP and PDAC by combining IgG4 and carbohydrate antigen 19-9 (CA 19-9) levels, with cutoff values of > 140 mg/dL and < 37 U/mL, respectively, obtaining

Table 1 Diagnostic criteria for autoimmune pancreatitis

Radiology	Serology	Histology	Response to steroid
Parenchyma:Diffuse enlargement with enhancement	IgG4 > 2 x upper limit of normal value	At least three	< 2 wk radiologically demonstrable resolution or marked improvement pancreatic/extrapancreatic manifestations
Duct: > 1/3 length of the main pancreatic duct		Periductal lymphoplasmacytic infiltrate without granulocytic infiltration	
Atypical: Segmental/focal narrowing with duct < 5 mm		Storiform fibrosis	
Other organ involvement: Bile duct: Segmental/multiple proximal or distal stricture		Obliterative phlebitis	
Retroperitoneal fibrosis		> 10 IgG4-positive cells/high power field	
Salivary/lachrymal glands: Symmetrically enlarged			
Renal involvement			

IgG4: Immunoglobulin G4.

a sensitivity of 64%, specificity of 92%, and diagnostic accuracy of 82 %. When the authors increased the cutoff to 280 mg/mL for IgG4 and 85 U/mL for CA 19-9, they reported a higher diagnostic accuracy of 86.9%. These results differ from those described by van Heerde *et al*[15], who considered less strict cutoff levels (1 g/L for IgG4 and 74 U/mL for CA 19-9) and obtained a sensitivity of 94 % and specificity of 100 %. These discrepancies highlight the need to study large samples of patients with homogeneous clinical characteristics to ensure the reproducibility of data on diagnostic accuracy. However, the search for new biomarkers is hampered by the fact that AIP is a rare entity, limiting sample sizes. In this review, we summarize and discuss the progress made in the search for new serum biomarkers for the diagnosis of AIP.

CLASSIC SEROLOGICAL MARKERS IN AIP AND PDAC

IgG4

IgG4 is the only serological biomarker currently included in diagnostic criteria for AIP, specifically type 1 AIP[7]. Values above 135-140 mg/dL were previously established as the cut-off point for the diagnosis, varying in sensitivity and specificity according to the population under study[16].

Absolute values are not taken into account in the diagnosis because of the interlaboratory variability in normal values, and patients are considered positive when their IgG4 concentrations are two-fold higher than the upper limit of normality[17]. European guidelines on IgG4 disease published in 2020 describe the IgG4 concentration has having diagnostic value when concentrations are four-fold higher than the upper limit of normality, which is only observed in a minority of patients[18]. Indeed, when jaundice secondary to a pancreatic mass is present, only a value 92-fold higher than the upper limit of normality is considered strongly suggestive of AIP[7].

Besides its elevation in PDAC patients[8,19], the usefulness of this serum biomarker is also reduced by its lack of specificity and sensitivity to differentiate between primary sclerosing cholangitis and cholangiocarcinoma, which can increase the false positive rate by up to 40%[20]. Serum IgG4 is also not useful for the diagnosis of type 2 AIP associated with inflammatory bowel disease[16] and must be accompanied at least by suggestive radiological findings to have diagnostic value in AIP[21]. Finally, normal IgG4 concentrations have been reported in up to 20% of AIP patients, even in the active phase [22].

CA 19-9

CA 19-9 is a tumor marker that is detectable in serum and widely used in the clinical management of PDAC[23]. CA 19-9 is elevated in the majority of PDAC patients and is useful for monitoring purposes; however, this biomarker is not useful for the early diagnosis of PDAC detection because of the substantial number of false positives and negatives[24].

Furthermore, CA 19-9 is commonly elevated in AIP patients, almost 40% of whom have concentrations above 100 U/mL[15]. In this way, individual measurements of either CA 19-9 or IgG4 are unable to distinguish AIP from PDAC[25].

The numerous limitations of CA 19-9 include the influence on its concentrations of the presence of jaundice and cholangitis, among many other factors. Nevertheless, it is widely used because it is accessible and cheap, and the sensitivity and specificity can be improved by its combination with other clinical, serological, histological and/or morphological criteria[26].

Hence, the combination of various serological biomarkers appears necessary to distinguish between AIP and PDAC. In this line, Yan *et al*[27] proposed combining CA 19-9 with globulin, eosinophils, and hemoglobin for the differential diagnosis. Elevated concentrations of eosinophils and globulin together with reduced concentrations of Hb and CA 19-9 were found to identify patients with AIP with a sensitivity of 92% and specificity of 79%, a relatively high diagnostic value.

NOVEL SERUM BIOMARKERS PROPOSED FOR THE DIFFERENTIATION OF AIP FROM PDAC

Igs

IgG1 and IgG2 have been studied in relation to AIP. IgG1 has been proposed as a diagnostic marker for AIP and IgG4-associated disease due to its involvement in the immunogenesis of the disease[28]. However, IgG2 concentrations were lowest in AIP and highest in IgG4-associated disease with orbital involvement[29].

There are different glycoforms of IgG subclasses, and different patterns of glycosylation have been described between patients with AIP and PDAC. Quantitative analysis of the IgG glycosylation profile may therefore allow the differential diagnosis between these entities to be established with high precision[30].

In addition, the proportion of different types of Igs has also shown some promise as a biomarker. An increase in IgG and inversely proportional reduction in IgA and IgM have been reported in AIP and IgG4-associated disease. In addition, elevated IgE has been described as having diagnostic and prognostic value for disease relapse in both entities[31].

Autoantibodies

Anti-annexin A11, anti-laminin 511-E8, and anti-galectin-3 autoantibodies have been implicated in the pathogenesis of AIP over recent years. Hubers *et al*[32], proposed annexin 11, a calcium-dependent phospholipid-binding protein, as an autoantigen in AIP. They showed that annexin A11-specific IgG4 competitively inhibited the pathogenic binding of annexin A11-specific IgG1 to shared epitopes, suggesting that the IgG1-mediated pro-inflammatory response could be downregulated by IgG4. Laminin 511-E8 is a truncated form of laminin 511, which is part of the extracellular matrix of the pancreas. Shiokawa *et al*[33] detected laminin 511-E8 in 51% of AIP patients (n = 51) compared with 1.6% of controls (n = 122) and suggested that it is an autoantigen in this disease. Galectin-3, which has been associated with fibrotic disorders, has also been proposed as a candidate biomarker[34]. In addition, anti-trypsinogen autoantibodies have been observed in sera from AIP patients and related to the loss of acinar cells[35].

Autoantibodies to amylase-2A and heat-shock protein 10 (HSP10) were previously found to be present not only in AIP but also in fulminant type 1 diabetes. Amylase-2A autoantibodies have not been detected in toxic CP or PDAC, while anti-HSP10 antibodies have been reported in a small percentage of patients[36,37].

Anti-plasminogen-binding protein autoantibodies have been observed in almost 95% of AIP patients (n = 35). Interestingly, these antibodies were presented by IgG4-negative patients with AIP but not by IgG4-positive patients with type 2 AIP[38]. Anti-pancreatic secretory trypsin inhibitor has also been suggested as a potential AIP-specific antibody, although it was detected in serum from less than half of AIP patients[39].

Other proposed autoantibodies have been those against carbonic anhydrase II, but they are not AIP-specific and are observed at high levels in other disorders such as Sjögren's syndrome[40]. In the same way, high concentrations of anti-lactoferrin antibodies have been described in immune diseases other than AIP such as ulcerative colitis[41], and anti-prohibitin antibodies are detectable not only in AIP patients (73.5%, n = 34) but also in patients with Mikulicz's disease (53%, n = 15%) or retroperitoneal fibrosis (54%, n = 11)[42].

Felix *et al*[43], studied the spectrum of autoantibodies in patients with AIP (n = 14 with type 1 and 11 with type 2) or PDAC (n = 26) and healthy controls (n = 22), showing elevated titers of both novel and previously reported antibodies against a variety of autoantigens, including carboxypeptidase A1 precursor, procarboxypeptidase A2, trypsin-1-preproprotein, and vimentin, among others. The authors found 68 autoantigens in AIP, 26 in PDAC and 21 in both diseases. The researchers selected 13 autoantibodies with potential to discriminate between the two types of AIP and also proposed antitransaldolase antibody as a biomarker to differentiate between type 2 AIP and PDAC.

Chemokines and cytokines

The Th2 immune response is a prominent feature of AIP, and some Th2 chemokines might therefore be useful as AIP biomarkers. Increased serum concentrations of C-C Motif Chemokine Ligand 17 have been reported in patients with IgG4-related disease, but this biomarker has not been explored in AIP [44].

Increased expressions of C-X-C motif chemokine ligand (CXCL) 9 and CXCL10 were recently demonstrated in an experimental model of AIP, but data on their concentrations in patients are not yet available[45].

Th2 cytokines have also been proposed as AIP biomarkers. Thus, interleukin (IL)-5 was found to be upregulated in patients with IgG4-related sclerosing cholangitis and suggested as a biomarker of AIP [46].

Serum concentrations of interferon (IFN)-alpha and IL-33 were found to be higher in patients with AIP than in those with chronic alcoholic pancreatitis or healthy controls. These concentrations were positively correlated with the serum concentrations of IgG4 antibodies. In addition, the observation of decreased IFN-alpha and IL-33 after treatment with corticosteroids, unlike IgG4 concentrations, suggests that they may be useful for following the response to treatment[47].

In a very interesting study, Ghassem-Zadeh *et al*[48] investigated the serum cytokine profile of patients with AIP (n = 29), CP (n = 17), and PDAC (n = 27) and its capacity to discriminate AIP from the other conditions. The authors found that serum levels of IL-1 beta, IL-7, IL-13, and granulocyte colony-stimulating factor (G-CSF) were higher in patients with AIP *vs* PDAC. The best diagnostic utility to differentiate AIP from PDAC was shown by IL-7 alone [area under the curve (AUC) = 0.780], obtaining a marginal added value when it was combined with G-CSF (AUC = 0.782). In the same line, G-CSF alone evidenced a better capacity to identify patients with CP from those with AIP (AUC = 0.804). In addition, the expression of tumor necrosis factor was found to be higher in PDAC tissue lysates than in either type of AIP.

Other cytokines suggested as potential AIP biomarkers include B cell-activating factor and proliferation-inducing ligand, which were found to be higher in patients with AIP than in healthy controls [49]. A decrease in these cytokines has also been observed after treatment with corticosteroids[45].

CONCLUSION

AIP and PDAC often course with similar symptoms, and biomarkers that can differentiate between them are needed for early initiation of the appropriate clinical action protocol. If this milestone is reached, it will be possible to avoid pancreatic resection in patients with AIP and incorrect steroid treatment in patients with PDAC.

Serum markers may be useful in patients with the presence of compatible symptoms and radiological findings, which have a low positive predictive value. Thus, some symptoms, such as abdominal pain and diabetes, may be present in both entities.

In addition, radiological criteria for suspicion of AIP are frequently not all present to establish a given diagnosis. Given the improved safety and performance of histological sampling of the pancreas by endosonography, this procedure should be added in cases of diagnostic doubt. However, the absence of malignancy does not definitively rule out neoplasia and, in the absence of histological criteria for a definitive AIP diagnosis, active suspicion of neoplasia should be maintained. In this context, the combination of serum biomarkers with all these tests can have a high qualitative and quantitative value to achieve a reliable diagnosis in these patients. This review describes serological biomarkers proposed for this purpose.

Increased serum concentrations of IgG4 antibody are a feature of AIP, but there are two main drawbacks to its usefulness as optimal AIP biomarker: (1) It is elevated in PDAC patients; and (2) It is not increased in a fraction of AIP patients. These problems have been addressed by numerous studies of new biomarkers for AIP diagnostics. These include biomarkers related to AIP immunopathogenesis, such as certain cytokines and chemokines, which have shown usefulness in research involving a small number of patients, although most studies did not examine the presence of these biomarkers in patients with PDAC. Some potential biomarkers have also been identified in experimental models but need to be tested in humans.

Another aspect to highlight is that, given the nature of these diseases, the use of a single serum biomarker is unlikely to accurately differentiate between AIP and PDAC. As observed in this study, almost all authors propose the utilization of a set of biomarkers to achieve high specificity and sensitivity for their reliable differentiation.

Translational application in this field will be achieved over the medium term, but further research is required on the numerous biomarkers proposed to date, recruiting larger samples of patients with AIP and assessing their presence in patients with PDAC. This is needed to verify their true specificity and to analyze their possible application in combination with clinical symptoms and/or radiological tests to achieve accurate differentiation between AIP and PDAC.

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