Typically, this complication is linked to a proliferative macroglobulinemia.[3,4,6]

SB is a rare cutaneous mucinosis of unknown pathogenesis first described in 1902[7,8] and classified in three clinical groups. Type II has been found to be associated with monoclonal gammopathy, multiple myeloma or B-cell lymphoma. Patients present non-pitting induration of the skin, preferably of the neck, face, chest or upper-arms. Histopathological study shows thickened collagen bundles separated by clear spaces. Histochemical stains demonstrate deposition of alcian blue positive, PAS-negative material consistent with acid mucopolysaccharides. Direct immunofluorescence is negative for immunoglobulin deposition. We found a unique case describing the association between WM and SB in the literature.[8]

Other identified mechanisms include organized IgM deposition (Type I cryoglobulinemia[9]), IgM-specific autoimmune manifestations (direct targeting of the skin in bullous dermatosis,[10] or immune complexes in type II and type III cryoglobulinemia and xanthomatosis[11]) or inappropriate cytokine secretion (Schnitzler syndrome).

This is the first case of two dermatological occurrences diagnosed in a patient with WM. It highlights the importance of recognizing such manifestations as they can precede or reveal a progressive or relapsing disease. In the absence of a known IgM monoclonal gammopathy, a search for a monoclonal component secreted by an indolent clone should be performed in the presence of such manifestations, in the setting of MGCS.

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Insulin resistance, mTOR and hidradenitis suppurativa

Dear Editor,

We read with great interest the original article by Vilanova *et al.*[1] and we completely agree that patients with hidradenitis suppurativa (HS) have a significantly higher prevalence of insulin resistance, as previously shown in our experience.

Our study has analysed homoeostasis model assessment of insulin resistance (HOMA-IR) in HS and healthy subjects with patients having higher values ($P = 0.023$). Moreover, we have assessed rate of glucose and insulin secretion after oral glucose tolerance test (OGTT). HS patients showed a significant difference, regarding insulin but not glucose rate, with respect to healthy subjects. Similarly to the results found by Vilanova[1], HS subjects affected by insulin resistance showed a correlation with disease severity as well as among the latter one and BMI.

Since mammalian target of rapamycin (mTOR) is involved in a number of either inflammatory or neoplastic conditions and its activities are also reported to be altered in metabolic as well as in autoimmune disorders,[2] we have investigated mTOR gene expression in HS patients, showing increased levels in lesional as well as non-lesional skin of HS patients compared to normal skin of healthy controls, with a strong correlation to disease severity.[3] Furthermore, an intense correlation was found between mTOR gene expression and serum insulin during OGTT at 30 as well as 60 min in HS subjects. Recent studies have established that increased activity of mTOR may lead to abnormal lipid metabolism and diabetes progression.[4] According to published results, we have suggested that mTOR might represent a molecular marker that is affected by the severity of HS and might be associated with insulin resistance. Besides, it is

likely to assume that mTOR levels may vary in relation to therapeutic response. Taking into account the high prevalence of obesity as well as metabolic syndrome in HS patients, especially in some countries, we strongly believe that it is necessary to evaluate glucose metabolism in all HS patients.[5]

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mTORC1 at the crossroad of metabolism and immunity in hidradenitis suppurativa

Editor,

We read with interest the paper by Vilanova *et al.*[1] reporting that the prevalence of insulin resistance (IR) was significantly higher in hidradenitis suppurativa (HS) patients compared with healthy controls. These results confirm the findings previously published by one of us (VDV) in the 2016 September Issue of JEADV.[2] The authors also discussed about the molecular mechanisms leading to a higher prevalence of IR in HS. In this regard, we think that dysregulation of mTORC1 signalling is the key event resulting in increased IR in HS, as suggested by the increased mTORC1 activity as well as by the correlation between mTORC1 activity and IR in HS patients.[2]

mTORC1 activates S6 kinase (S6K). S6K, in turn, causes phosphorylation and degradation of insulin receptor substrate 1/2 (IRS1/2), thus impairing insulin signalling.[3] In addition, mTORC1 causes IR by affecting growth factor receptor-bound protein 10 (Grb10)[3] (Fig. 1).

Of note, HS is significantly associated with an increased prevalence of diabetes mellitus (DM).[4] Type 2 DM is characterized by peripheric IR as well as defective insulin secretion. Interestingly, mTORC1 overactivation also contributes to impair β-cells function. Glucose activates mTORC1, thus inducing expansion and hypertrophy of β-cells as well as increased insulin secretion. β-cells hyperfunction compensates for insulin resistance and prevents hyperglycaemia. Subsequently, β-cells hyperfunction leads to their failure and manifest diabetes. In fact, prolonged overactivation of mTORC1 results in a predominant S6K negative feedback loop with decrease in IRS1/2 levels and reduction of IRS2/PDX1 pathway, fostering β-cells death.[3]

Furthermore, the mTORC1 pathway is of pivotal importance for metabolic regulation of innate and adaptive immunity, as shown by the immune-suppressive effects of mTORC1 inhibitors such as rapamycin. In particular, mTORC1 promotes Th17 differentiation[3] (Fig. 1). Th17 substantial infiltration in lesional skin and increased IL-17 serum levels have been found in HS patients. Interestingly, IL-17 also plays a key role in insulin resistance and DM. IL-17 deficiency increased glucose tolerance and insulin sensitivity in young mice. Obesity is one of the main known causes of DM development and is characterized by increased plasma concentrations of insulin, IGF-1 and IL-17. Serum IL-17 is significantly higher in DM patients than in controls.[3]

IL-1β and IL-18 are other key pro-inflammatory cytokines belonging to the IL-1 family and are involved in the pathogenesis of both HS and DM.[5,6] Their inactive precursors pro-IL-1β and pro-IL-18 are cleaved into the active forms IL-1β and IL-18 by caspase-1. A critical step for the autocatalytic self-cleavage of procaspase-1 into its active form is the assembly of a multiprotein complex called inflammasome and composed of procaspase-1, ASC and NLRP3. Intriguingly, mTORC1-induced glycolysis represents an essential metabolic process for NLRP3 inflammasome activation in macrophages (Fig. 1). Downregulation of glycolysis by inhibition of mTORC1 suppresses caspase-1 activation in macrophages and subsequently pro-IL-1β and pro-IL18 maturation.[6] Macrophages play a critical role in DM as well as in HS.[7,8] It is worth underlining that the dysregulation of the mTORC1 signalling promotes and sustains macrophage polarization towards a pro-inflammatory phenotype.[8]

Finally, TNF-α, which acts as a pivotal cytokine in HS immunopathogenesis, activates IκB kinase (IKK)-β. IKK-β, in turn, inactivates the mTORC1 negative regulator TSC1 (Fig. 1). Thus, TNF-α impairs insulin signalling and contributes to IR.[5] Consequently, the anti-TNF agent adalimumab – which is the first and only medication approved for HS – also decreases

