

# Disseminated gonococcal infection and the inaugural diagnosis of latent autoimmune diabetes in a young adult

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## ABSTRACT

Disseminated gonococcal infection (DGI) is a rare and emerging disease that should be considered in individuals who present with acute polyarthralgias, skin lesions and/or tenosynovitis, even in the absence of genitourinary symptoms.

We describe a 29 years old man presenting with fever, arthralgias, skin lesions and signs of tenosynovitis. The diagnostic approach identified a disseminated gonococcal infection and an unrecognized and latent autoimmune diabetes.

We emphasize not only the particularities of diagnostic and treatment approach currently required by this emergent infection, but also the importance of investigation of rare risk factors associated with an underlying immunosuppression. In latent autoimmune diabetes of adults a timely recognition and individualized treatment are fundamental for prognostic.

**Keywords:** Disseminated gonococcal infection, *Neisseria gonorrhoeae*, Tenosynovitis, Latent autoimmune diabetes in adults, Diabetes mellitus.

## CASE DESCRIPTION

A previously healthy 29-year-old man presented to the emergency department complaining of fever, asthenia and migratory arthralgias of wrists, fingers, ankles and toes that started in the previous two days. He also reported swelling of wrists and ankles and painless non-pruritic vesiculopustular skin lesions on both hands thenar eminence. He noted asthenia and a 7 Kg weight loss in the last 6 months. He didn't report neurologic, respiratory, digestive or genitourinary symptoms.

He was single, heterosexual and his last sexual contact had been one month before admission and protected but he recorded multiple partners last year. He worked as a butcher and denied exposure to drugs, ticks, animals or recent travels.

At admission, physical examination revealed a temperature of 39°C. Cardiac, pulmonary, abdominal and neurologic evaluations didn't show relevant changes. The skin examination revealed macules with central hemorrhagic pustule zone on both hands thenar eminence (Fig 1) and signs of tenosynovitis of both wrists and ankles (Fig.2). There were no signs of meningeal, ocular, genitourinary or rectal involvement. Body mass index (BMI) was 26 kg/m<sup>2</sup>.

Laboratory findings reported normocytic anemia (Hgb 11,5 g/dL; normal 13.5-18.0 g/dL), leukocytosis with neutrophilia (17.5 K/ $\mu$ L; normal 4-10 K/ $\mu$ L; 80%), an elevated erythrocyte sedimentation rate (ESR) (90mm/hr) and C-reactive protein (CRP) (98,6 mg/L). Renal, thyroid and liver function test results didn't show any changes and urinary study was normal. Thoracic x-ray, abdominal and renal ultrasound didn't show any active or suspicious lesion. Blood and urine cultures were performed and he was admitted to the internal medicine department.

As he maintained fever, polyarthralgias with signs of tenosynovitis and skin lesions, an infectious and serological study was required. Venereal disease research laboratory (VDRL) and tests for human immunodeficiency virus (HIV) 1 and 2 (including antibody test and rapid plasma reagin test), Cytomegalovirus (CMV), Herpes simplex virus (HSV), Epstein-Barr virus (EBV), Parvovirus and Hepatitis (A, B and C) were negative. Serology and culture tests for Rickettsia, Coxiella and Borrelia were also negative.

Immunological study through the search for autoantibodies (anti-nuclear antibody, anti-double stranded (ds) DNA, anti-neutrophil cytoplasmic antibodies (ANCA), anti-antinuclear antibody (ANA), Anti-Sjögren's-syndrome-related antigen A (AntiSSA), AntiSSB, Anti-ribonucleoproteins (RNP), and anti-citrullinated peptide antibody) and rheumatoid factor were negative. Coagulation and cardiac studies (including NT-proBNP and troponin I levels) were normal. Transthoracic Echocardiogram and ECG didn't reveal alterations.

On the third day after admission blood cultures revealed the presence of gram-negative diplococci and 5 days later, *Neisseria gonorrhoeae* was isolated in blood cultures processed on specific (Thayer-Martin) medium (Fig.3).

Imaging via ultrasound showed a moderately sized simple left ankle effusion with marked surrounding edema. Left ankle arthrocentesis was performed, revealing a mildly elevated synovial fluid White Blood Cell count of 30,800 cells/ $\mu$ L (normal below 2,000 cells/ $\mu$ L), and culture of the collected synovial fluid on specific (Thayer-Martin) medium showed no growth.

Mucosal including skin, rectal, pharyngeal, and urethral specimens were submitted for microbiological testing with Nucleic acid amplification tests (NAATs) and only the urethral specimen was positive.

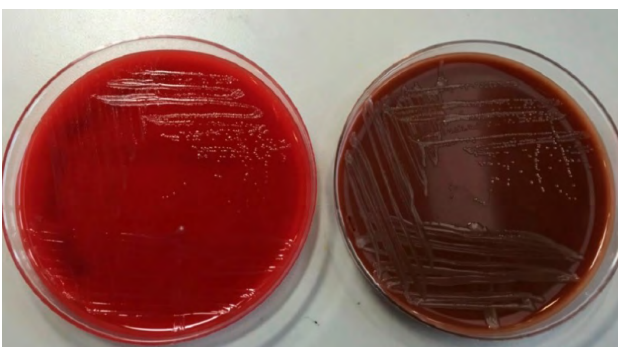
Figure 1. The skin examination revealing skin lesion with central hemorrhagic pustule zone on the palmar face of the right hand.



Figure 2. Inflammatory signs of the left ankle visible on admission and associated with pain and edema.



Figure 3. *Neisseria gonorrhoeae* was isolated in blood cultures processed on specific (Thayer-Martin) medium.



In regard to emerging antibiotic resistance of *N.gonorrhoeae* (to cephalosporins and azithromycin), an antibiotic susceptibility test (AST) was also performed and he started single dose of azithromycin plus ceftriaxone intravenous 1g/day, completing 7 days of antibacterial therapy. Three days later, AST revealed all strains susceptibility to ceftriaxone, cefepime, cefotaxime and quinolones. Serologic test for syphilis, and NAATs of Chlamydia were negative.

DGI was notified and the identified partners were offered with treatment for both gonococcal and chlamydial infections.

In regard to the apparent absence of some specific host risk factors for DGI and based on association of this systemic presentation with possible immune factors, a study for complement deficiency and immunoglobulins was performed, and was negative. (Complement C3 fraction - 170 mg / dL (VN 90-198); Fraction C4 of complement - 31 mg / dL (VN 10-40); CH50 - 38 mg / dL (NV > 24).

Despite favourable clinical and analytical evolution, it was documented several low magnitude postprandial and basal hyperglycemias (250-300 mg/dl) and after evaluation of endocrinology, Latent autoimmune diabetes in adults

(LADA) was suspected. He was discharged 2 weeks later with insulin therapy. One month after, he was asymptomatic, with negative blood cultures and the diagnostic approach revealed positivity for autoantibodies anti-tyrosin-phosphatase and glutamic acid decarboxylase 65 (GAD65) with normal C-peptide values, supporting LADA diagnosis.

## DISCUSSION

This case report is remarkable by its rarity, distinct clinical manifestations, challenging diagnostic approach and surprising evolution. It discloses a previously healthy 31-year-old man, presenting with fever, artralgiias, skin lesions and signs of tenosynovitis. The diagnostic approach identified a disseminated gonococcal infection and an unrecognized and latent autoimmune diabetes.

### Disseminated gonococcal infection (DGI)

DGI affects 1-3% of patients with gonorrhoea and results of haematogenous spread of *Neisseria gonorrhoeae*, typically occurring within 2-3 weeks of the primary infection. It demands a difficult diagnostic approach not only because a recent symptomatic genital infection is rare, but also because positive blood cultures are found in only 50% of DGI cases that present with the classic triad of dermatitis, tenosynovitis and polyarthralgiias<sup>1-4</sup>. In this case report we emphasize the complete infectious, autoimmune and immunological study performed.

The disseminated form primarily affects young (15 and 30 years), healthy and sexually active individuals like this patient, nevertheless the study for other unrecognized immune factors or diseases as SLE or hypocomplementemia should be performed and was negative<sup>5-9</sup>.

However, based on several low magnitude postprandial and basal hyperglycemias, a surprising diagnosis of LADA was made,

which can explain the unrecognized immune factor responsible not only for immunosuppression but also for autoimmunity trigger. We highlight that this represents a relevant new association that has not yet been reported in previous scientific articles with a fundamental impact on the therapeutic approach.

Treatment of DGI depends on manifestations and clinical response. We emphasize the importance of susceptibility testing focused on emerging resistance to cephalosporins and azithromycin. For disseminated infections, combination and parental therapy treatment with ceftriaxone (1 g; 7 to 14 days) along with a single dose of azithromycin is recommended, also treating possible *C. trachomatis* co-infection<sup>1-2</sup>.

### Latent autoimmune diabetes in adults (LADA)

Latent autoimmune diabetes in adults (LADA) shares clinical and metabolic characteristics with both type 2 and type 1 diabetes and should be suspected on 30-50-years-old individuals, with BMI <25 kg/m<sup>2</sup>, low magnitude postprandial and basal hyperglycemia and normal or close to normal C-peptide values, not usually occurring with acute hyperglycemic crises<sup>10-13</sup>.

Patients defined as having LADA are characterized by genetic, phenotypic, and immunological heterogeneity, highly variability of the  $\beta$ -cell destruction's rate and different degrees of insulin resistance and autoimmunity, likely due to differences in genetic and immune factors<sup>14-16</sup>. Moreover, the great heterogeneity of LADA makes it difficult to determine an a priori algorithm for treatment and personalised therapy for LADA should be implemented<sup>14-20</sup>.

#### Pathogenesis

When compared with classical T1DM, LADA appears like the other extreme of the autoimmune diabetes spectrum, whereby genetic susceptibility, autoimmune response and non-insulin-necessity presentation constitute a mild form of autoimmune diabetes with pathological features closer to those of T2DM than to those of adult T1DM, which is more similar to classical T1DM<sup>10,17,18</sup>.

#### a) Genetic factors

Data available on genetic susceptibility suggest that LADA shows a lower genetic component than T1DM<sup>14,15,21</sup>. However, a recent study carried out in Swedish and Finnish populations, showed that the frequency of T2DM associated CT/TT genotypes rs7903146 in the transcription factor 7 like 2 (TCF7L2) gene was increased in LADA subjects as in T2DM subjects<sup>23</sup>, as well as genetic similarities with T1DM have been observed related to HLA, INS VNTR, and PTPN22. These results suggest that patients with LADA may share genetic features with both T1DM and T2DM which further supports the concept that LADA is an admixture of the two major types of diabetes<sup>22</sup>.

#### b) Autoimmunity

As a form of autoimmune diabetes, LADA is characterized by islet-cell specific autoantibody positivity and similar cell-mediated immune response although impairment of

$\beta$ -cells is slower than in classical T1DM<sup>10,12,18</sup>. Another relevant study observed presence of insulinitis by pancreatic scintigraphy using interleukin 2 (IL-2) radiolabelled with technetium-99m (99mTc) and contrast-enhanced magnetic resonance imaging<sup>24</sup>.

In conclusion and trying to investigate LADA pathogenesis, a recent Italian work suggested that different pathophysiological could explain the heterogeneous phenotypes of LADA<sup>17</sup>. Based on the model presented, in patients with moderate genetic susceptibility to T1DM, specific immunological factors can trigger an autoimmune process against islet cell antigens marked by the appearance of GADAs leading to  $\beta$ -cell apoptosis and insulin deficiency. On the other hand, in obese subjects with genetic susceptibility to T2DM, the low-grade inflammation, typical of visceral adiposity, might trigger a low-grade autoimmune process marked by IA-2 autoantibodies positivity, causing loss of  $\beta$ -cell function and an impairment of insulin secretion.

Regarding our case report we can theorize the importance and significance of infection as trigger factor for insulinitis with consequent insulin deficiency and LADA onset. However, given the temporal coincidence, the causal relation can not be concluded, since the patient already had symptoms associated with diabetes and it is impossible to date the beginning of the infection as well as gonococcus dissemination.

#### Natural history and complications

There are only few studies related to the occurrence of macro and microvascular complications (nephropathy, retinopathy, neuropathy) in LADA and controversial results have been reported, partly due to a substantial heterogeneity regarding disease duration of study's subjects. Limited to patients with a short disease duration, microvascular complications in LADA appear to be less frequent than in patients affected by T2DM. A lower risk of macrovascular complications—including coronary heart disease, stroke, peripheral artery disease—could be postulated on the basis of the healthier metabolic profile of patients with LADA respect to those with T2DM. However, current data showed similar cardiovascular outcomes in LADA and T2DM<sup>25-27</sup>.

Nevertheless, this case report highlights the importance of infection susceptibility associated with LADA, disclosing a patient without another identified host factor, diagnosed with a severe disseminated gonococcal infection, that could bring potential severe complications and evolution, beyond possible treatment difficulties regarding bacterial antibiotic resistance.

#### Treatment

To date, no specific guidelines for treatment of subjects affected by LADA have been published. Therefore, these subjects are mostly treated as affected by T2DM resulting in rapid progression to an insulin-dependent state<sup>17</sup>, especially in patients who present with clinical and biochemical features closer to T1DM than T2DM<sup>28,29</sup>. In addition, a correct therapeutic strategy for LADA patients should aim to the preservation of residual  $\beta$ -cell function as well as improvement of glucometabolic control, in order to reduce the risk of long-term complications. Main-



tenance of  $\beta$ -cell function, as demonstrated by the Diabetes Control and Complication Trial, is indeed associated with a reduction of long term diabetic complications<sup>29</sup>.

In this regard, several data showed that insulin treatment, as well as DPP-4 agents, can sustain residual  $\beta$ -cell function<sup>30-38</sup>. Insulin therapy (basal), at low dose can be prescribed to LADA patients with DPP-4 as an additional weapon, whereas sulphonylurea may hasten insulin dependency and should not be used as first-line therapy for patients with LADA.

#### *Preservation of $\beta$ -cell function: next frontiers in LADA therapy*

An intervention intended to preserve  $\beta$ -cell function should be pursued in patients with LADA. Recent immune-intervention trials have achieved promising results in term of preserving stimulated C-peptide levels and improving glycaemic control. However, some drugs currently used for treatment of T2DM might be considered in LADA. Dipeptidyl peptidase 4 (DPP-4) inhibitors represent a class of oral antidiabetic agents frequently used in T2DM which have been shown to preserve  $\beta$ -cell function and reduce insulinitis in patients with T2DM as well as in mouse models of autoimmune diabetes<sup>30-34</sup>, suggesting that they might be a valuable treatment option in LADA.

A randomized-controlled study conducted in China<sup>33</sup> has observed that treatment with sitagliptin in addition to insulin preserved C-peptide concentration better than insulin alone in patients with LADA over a 1-year period. Similarly, sitagliptin improved glycaemic control in adults with T1DM<sup>34</sup>. Furthermore, Johansen et al.<sup>35</sup> have reported that another DPP-4 inhibitor, linagliptin, attenuated decline of C-peptide in LADA patients over a 2-year study period. In a post hoc analysis of data pooled from five randomized, placebo-controlled studies<sup>36</sup>, saxagliptin was effective in lowering blood glucose levels and well tolerated in GADA-positive patients.

Other interesting findings comes from a post hoc analysis investigating treatment with dulaglutide, a glucagon-like peptide 1 receptor agonist (GLP-1RA)<sup>37</sup> in patients with T2DM among whom there were some GAD antibody positive patients.

As conclusion, in this report we emphasize the importance of LADA diagnosis, supported by positivity for autoantibodies anti-tyrosine-phosphatase and GAD65 and the importance of DGI as a trigger for autoimmunity and insulinitis, which can represent a pathogenesis mechanism in LADA development. Although the possible association between LADA and infection can be suspected, given the temporal coincidence, a causal relation can not be established. On the other hand, we underline the possible association of LADA with greater infection susceptibility and severity in the natural history of the disease, as well as potential impact in antibiotic treatment and bacterial antibiotic resistance.

Finally, we highlight that personalized, controversial and under recent investigation medicine approach to attain optimal metabolic control is fundamental to preserve  $\beta$ -cell function decreasing the risk of long-term diabetes complications.

## LEARNING POINTS

- The possibility of Disseminated gonococcal infection (DGI) should be considered in individuals who present with acute polyarthralgias, skin lesions (particularly pustular or vesiculopustular) and/or tenosynovitis, even in the absence of genitourinary symptoms.
- The study of an underlying immunosuppression and the treatment of DGI after appropriate cultures and based on emergent antibiotic resistance is essential and patients should be tested for HIV infection, syphilis and chlamydia.
- Latent autoimmune diabetes in adults (LADA) should be investigated in > 30-years-old individuals with low magnitude postprandial and basal hyperglycemias, with appropriate diagnostic approach, demanding an updated treatment.

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