Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Title:
Can flow cytometry be a key in the difficult diagnosis of coeliac disease?

Authors:
Andrés Castañeda, Marta Álvarez García, Cristina Serrano del Castillo, Raquel Téllez Pérez , Ana Pilar Lanzarote Vargas , María José Romero Valle, Lonore Hurtado de Mendoza, Sergio Farrais Villalba

DOI: 10.17235/reed.2024.10833/2024
Link: PubMed (Epub ahead of print)

Please cite this article as:
Castañeda Andrés, Álvarez García Marta, Serrano del Castillo Cristina, Téllez Pérez Raquel, Lanzarote Vargas Ana Pilar, Romero Valle María José, Hurtado de Mendoza Lonore, Farrais Villalba Sergio. Can flow cytometry be a key in the difficult diagnosis of coeliac disease? . Rev Esp Enferm Dig 2024. doi: 10.17235/reed.2024.10833/2024.

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Can flow cytometry be a key in the difficult diagnosis of coeliac disease?

Castañeda Agredo Andrés[1], Álvarez García Marta[1], Serrano Del Castillo Cristina[2], Téllez Pérez Raquel[2], Lanzarote Vargas Ana[1], Romero Valle María José[1], Hurtado de Mendoza Lonore[1], Farrais Villalva Sergio[1]

Department of Gastroenterology and Hepatology[1]. Department of Clinical Inmunology[2]. Hospital Universitario Fundación Jiménez Diaz. Madrid, Spain.
Correspondence: Andrés Castañeda. E-mail: andres.castaneda@quironsalud.es

Keywords: Citometry. Coeliac. Seronegative.

Dear Editor,

Flow cytometry (FC) is a diagnostic technique in which different cell types are labeled with specific fluorescent antibodies, allowing for rapid and precise cell counting based on their physical and chemical characteristics. In the context of celiac disease (CD), where diagnosis can be challenging, especially in seronegative celiac disease (SNCD), this technique provides an additional diagnostic tool that allows for the determination of intraepithelial lymphocytes (IELs) subpopulations in the duodenal epithelium with a characteristic celiac pattern, showing high diagnostic accuracy for CD (S87%, E96.7%, VPP 92%). However, it is important to first rule out conditions that can mimic celiac enteropathy.

Histology and serology are traditional methods that provide morphological information and show the presence of positive antibodies in patients with CD. Despite this, patients with SNCD are characterized by having typical histological lesions that reverse after gluten withdrawal, but with an absence of positive serology for CD. In this case, the need for additional tests can provide essential information for the final diagnosis of CD.

We present the case of a 39-year-old woman with a medical history of juvenile idiopathic arthritis and uveitis, evaluated for abdominal pain, distension, difficulty gaining weight, and diarrhea lasting several years. Blood tests revealed negative antibodies (TTG IgA <0.5, DGP

IgA 1.1) and showing positivity for HLA DQ 7.5, indicating the lowest genetic risk for CD. A gastroscopy with duodenal biopsies revealed findings consistent with stage 3b of the modified Marsh classification (Fig. 1 above). Due to diagnostic uncertainty, an IEL study was performed, revealing a characteristic CD pattern (Fig. 1 middle) and prompting the initiation of a strict gluten-free diet. During follow-up, the patient exhibited partial improvement, with persistent digestive symptoms. A repeat endoscopic study showed persistent atrophy, and refractory type 2 disease was ruled out. During a flare of her rheumatologic disease, Tocilizumab was initiated, leading to improvement in duodenal atrophy.

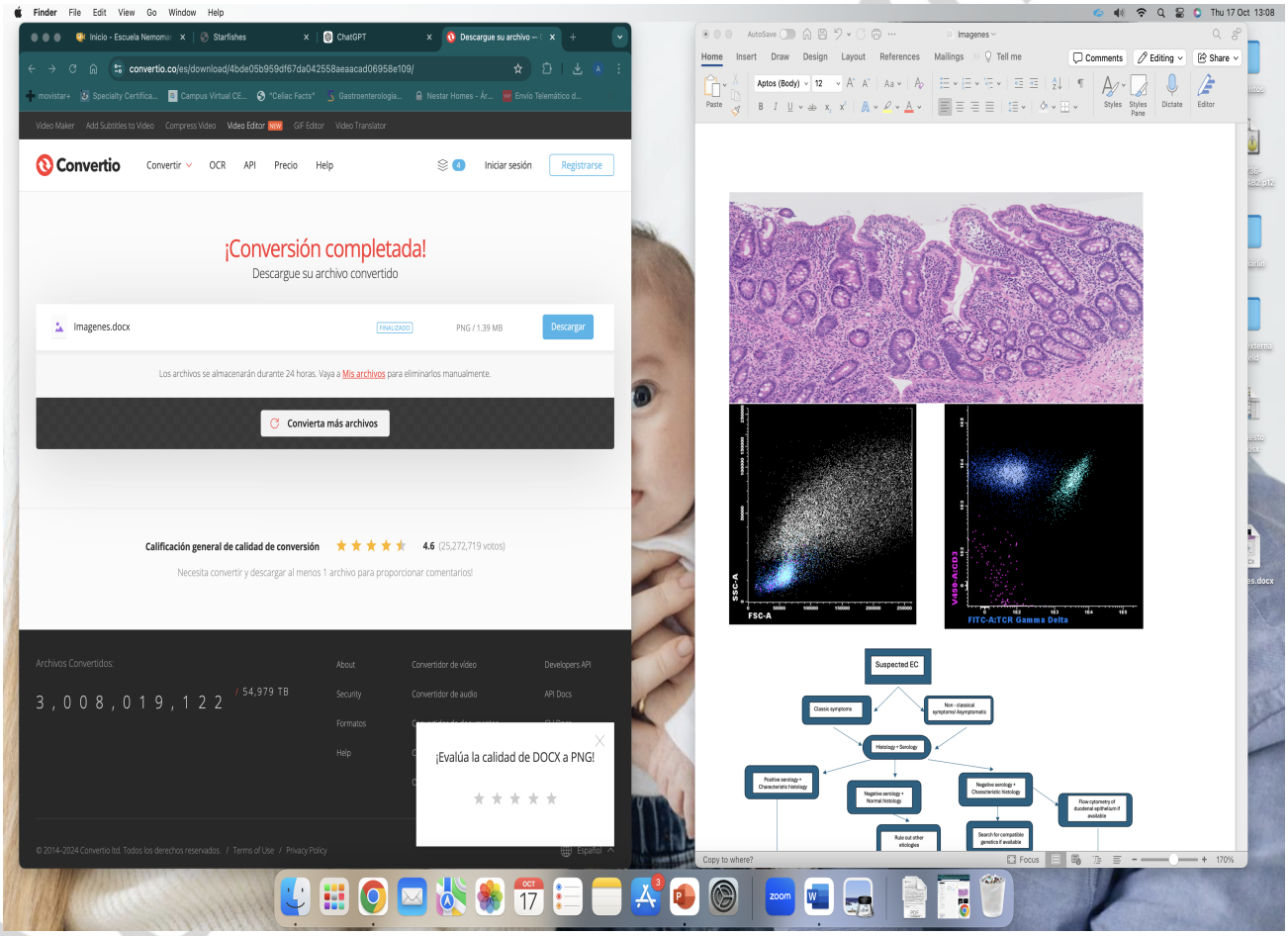
Proper identification and diagnosis of celiac disease in seronegative patients is crucial, as they often present with more severe disease activity. In this context, IELs serve as an important diagnostic tool. This technique is also useful for patients with CD without atrophy, uncertain cases, those on a gluten-free diet, or detecting aberrant lymphocytes. Despite its high diagnostic value, FC has limited availability, higher costs, and requires specialized staff. There is a pressing need for clinical trials or multicenter studies to further explore the efficacy of FC in asymptomatic patients. Such research could facilitate early detection and intervention, potentially reducing long-term complications associated with undiagnosed EC.

References

1. Pallav K, Leffler DA, Tariq S, Kabbani T, Hansen J, Peer A, Bhansali A, Najarian R, Kelly CP. Noncoeliac enteropathy: the differential diagnosis of villous atrophy in contemporary clinical practice. Aliment Pharmacol Ther. 2012 Feb;35(3):380-90
2. Grupo de trabajo del Protocolo para el diagnóstico precoz de la enfermedad celíaca. Protocolo para el diagnóstico precoz de la enfermedad celíaca. Ministerio de Sanidad, Servicios Sociales e Igualdad. Servicio de Evaluación del Servicio Canario de la Salud (SESCS); 2018.
3. Espino L, Nuñez C. Chapter two – The HLA complex and coeliac disease. International Review of Cell and Molecular Biology 2021; 358: 47-83.
4. Fernández-Bañares F, Crespo L, Núñez C, López-Palacios N, Tristán E, Vivas S, Farrais S, Arau B, Vidal J, Roy G, Esteve M. Gamma delta^{+} intraepithelial lymphocytes and

coeliac lymphogram in a diagnostic approach to coeliac disease in patients with seronegative villous atrophy. Aliment Pharmacol Ther. 2020 Apr;51(7):699-705.

5. Aziz I, Peerally MF, Barnes J-H, et al. The clinical and phenotypical assessment of seronegative villous atrophy; a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000–2015). Gut. 2017;66:1563-1572



Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

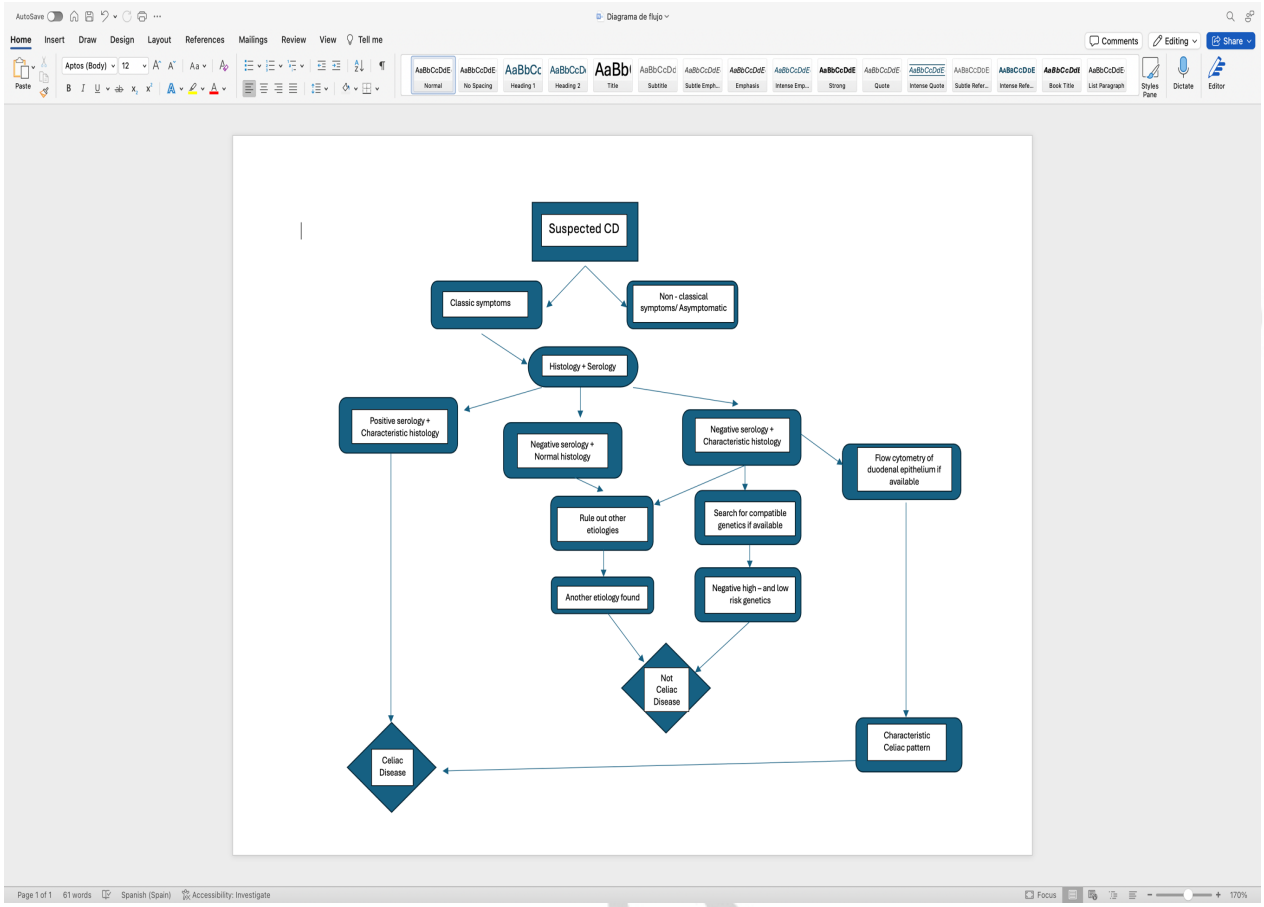


Figure 1. Above. Duodenal biopsy with intraepithelial lymphocytosis and severe villous atrophy. Figure 1. Middle. Intraepithelial lymphogram by flow cytometry showing an increase of IELs with a high proportion of TCR γδ T lymphocytes [right image]. Increased total IELs with proportional increase of TCRγδ T lymphocytes and decreased of CD3neg IELs (also known as NK-Like cells or innate T lymphocytes) [Left image]. Figure 1 Below. Proposed flowchart for the diagnosis of Celiac Disease with or without positive antibodies.