Letter to the Editor

Lack of association between the TNFAIP3 rs2230926 variant and rheumatoid arthritis-associated lymphoma

A R T I C L E   I N F O

Keywords:
Rheumatoid arthritis
Lymphoma
TNFAIP3
A20
Single nucleotide polymorphism

There is an increased risk of lymphoma in patients with autoimmune diseases (AID) especially rheumatoid arthritis (RA) and primary Sjögren Syndrome (pSS) with a respective relative risk of 2 and 15 [1]. The mechanisms promoting lymphomagenesis in AID might be diverse [2]. Disease activity and chronic antigenic stimulation of autoimmune B cells play a key role in lymphomagenesis associated with pSS [3]. In this context, a complete control of the NF-kB pathway activation is required to avoid B-cell clonal proliferation. TNFAIP3 encodes for the protein A20, a key gatekeeper of NF-kB activation and the TNFAIP3 rs2230926 variant was previously found to be associated with lymphoma in pSS [4,5]. This variant is responsible for a slight decreased control of NF-kB activation. In patients with RA, mechanisms leading to lymphoma occurrence, mainly diffuse large B-cell lymphoma (DLBCL), is less understood. From an epidemiologic point of view, it has been demonstrated that high cumulative RA disease activity increase odds for lymphoma [6]. Given the association of TNFAIP3 rs2230926 with the overall RA [7], and pSS-related lymphoma [4,5], we decided to investigate its contribution to RA-related lymphoma susceptibility.

To this end, a multicentre case-control study was performed. Cases were patients with RA fulfilling ACR-EULAR 2010 criteria, who developed a B-cell NHL or Hodgkin’s lymphoma after the diagnosis of RA. Controls were patients with RA and without lymphoma matched on age. Fifty-four cases of RA-related lymphoma were included and matched to 108 controls (1:2) [8]. DNA was available for 145/162 (89.5%) patients (38 cases and 107 controls), having no difference in demographic and disease characteristics compared to the whole study population (Table 1). Overall, 101 patients (69.2%) were female, with a mean age of 51.9 years (SD = 10.9) at RA diagnosis and a mean disease duration of 10.5 years (SD = 4.9). Lymphomas were mostly DLBCL (n = 19, 50.0%), follicular lymphoma (n = 6, 15.8%) and marginal zone lymphoma (n = 4, 10.5%). The genotyping study revealed no significant association between the TNFAIP3 rs2230926 variant and the occurrence of lymphoma (P = 0.30) (Table 2).

Even if this study could suffer from a relatively low power of detection (estimated power of 80%), this lack of association suggests distinct mechanisms of lymphomagenesis in RA and pSS.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole genotyping study population (n = 145)</th>
<th>Cases (n = 38)</th>
<th>Controls (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>45 (31.0)</td>
<td>20 (52.6)</td>
<td>25 (23.4)</td>
</tr>
<tr>
<td>Age at RA diagnosis, mean (SD)</td>
<td>51.9 (10.9)</td>
<td>49.8 (12.6)</td>
<td>52.7 (10.2)</td>
</tr>
<tr>
<td>Age at the time of matching, mean (SD)</td>
<td>62.0 (10.1)</td>
<td>61.2 (10.2)</td>
<td>62.2 (10.1)</td>
</tr>
<tr>
<td>ACPA positivity, n (%)</td>
<td>106 (73.1)</td>
<td>92 (25.6)</td>
<td>101 (90.3)</td>
</tr>
<tr>
<td>RF positivity, n (%)</td>
<td>111 (76.6)</td>
<td>92 (24.3)</td>
<td>118 (109.7)</td>
</tr>
<tr>
<td>Erosions on X-rays at the time of matching, n (%)</td>
<td>55 (37.9)</td>
<td>30 (14.9)</td>
<td>75 (59.7)</td>
</tr>
<tr>
<td>DAS28 at the time of matching, mean (SD)</td>
<td>2.9 (1.5)</td>
<td>3.9 (1.1)</td>
<td>2.6 (1.4)</td>
</tr>
<tr>
<td>RA duration at the time of matching, mean (SD)</td>
<td>10.6 (5.0)</td>
<td>11.0 (5.7)</td>
<td>10.0 (4.3)</td>
</tr>
</tbody>
</table>

IQR: interquartile range; ACPA: anti-citrullinated peptide antibodies; DAS28: disease activity score in 28 joints; RA: rheumatoid arthritis; RF: rheumatoid factor; the time of matching corresponded to the diagnosis of lymphoma for cases and the 10-year ESPOIR visit for controls.

Table 2

Testing for association of TNFAIP3 rs2230926 with RA-related lymphoma.

<table>
<thead>
<tr>
<th>TNFAIP3 rs2230926</th>
<th>Cases (n = 38)</th>
<th>Controls (n = 107)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAF</td>
<td>2.6%</td>
<td>5.6%</td>
<td>0.45 (0.10–2.08)</td>
</tr>
<tr>
<td>TT</td>
<td>36 (94.7%)</td>
<td>96 (89.7%)</td>
<td>0.49 (0.10–2.30)</td>
</tr>
<tr>
<td>TG</td>
<td>2 (5.3%)</td>
<td>10 (9.3%)</td>
<td>0.53 (0.11–2.55)</td>
</tr>
<tr>
<td>GG</td>
<td>0 (0.0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MAF: minor allele frequency. Chi-square test. Differences between cases and controls were statistically non significant.

https://doi.org/10.1016/j.jbspin.2022.105390
1297-319X/© 2022 Société française de rhumatologie. Published by Elsevier Masson SAS. All rights reserved.
Lymphoma histology and localization differ in pSS and RA-associated lymphoma; MALT lymphoma of salivary glands in pSS versus nodal DLBCL in RA. RF positivity and/or cryoglobulinemia are associated with lymphoma occurrence in pSS but not in RA [3]. In RA, instead of a direct transformation of autoimmune B cells, lymphoma might derive from associated subsets of B cells such as memory B cells. Interestingly, memory B cells involved in RA are increased in longstanding disease [9]. Recently, TBL1XR1 rare variants were found to induce ABC DLBCL by promoting aberrant memory B cells, which are prone to avoid plasmocytic differentiation on recall and to undergo systemic dissemination [10].

In aggregates, we did not detect any association between the TNFAIP3 rs2230926 variant and RA-related lymphoma. This highlights the need for further studies to determine the specific mechanisms driving RA lymphomagenesis.

Disclosure of interest

The authors declare that they have no competing interest.

Funding details

The French Society of Rheumatology (Société Française de Rhumatologie–SFR) provided a grant to support the genetic analysis.

Espoir cohort

An unrestricted grant from Merck Sharp and Dohme (MSD) was allocated for the first 5 years. Two additional grants from INSERM were obtained to support part of the biological database. The French Society of Rheumatology, Abbvie, Pfizer, Lilly, and more recently Fresenius and Galapagos also supported the ESPOIR cohort study. We also thank Nathalie Rincheval for expert monitoring and data management and all the investigators who recruited and followed the patients (F. Berenbaum, Paris-Saint Antoine, MC. Boissier, Paris-Bobigny, A. Cantagrel, A. Constantin, Toulouse, B. Combe, Montpellier, M. Dougdas, Paris-Cochin, P. Boumier, Amiens, B. Fautrel, Paris-La Pitié, RM. Flipo, Lille, P. Goupille, Tours, F. Liote, Paris-Lariboisière, O. Vittecoq, Rouen, X. Mariette, Paris Bicêtre, Ph Dieude, Paris Bichat, A. Saraux, Brest, Th. Schaeverbeke, Bordeaux, J. Sibilia, Strasbourg). One biological resources centre (Paris-Bichat, S Tubiana) was in charge of centralising and managing biological data collection.

Funding

Supported by the French Society of Rheumatology (Société Française de Rhumatologie, SFR).

Contributorship statement

All authors have contributed to this work and have approved the final version of the manuscript.

Acknowledgements

The authors wish to acknowledge the French Society of Rheumatology (Société Française de Rhumatologie–SFR) for the grant provided to support the genetic analysis.

References

Joint Bone Spine 89 (2022) 105390

J. Kedra, R. Seror, P. Dieudé et al.

1 Rheumatology department, Brest university hospital, Brest, France
2 Department of rheumatology, University Hospital Gabriel Montpiède, Clermont-Ferrand, France
3 Rheumatology department, Fondation Hopale, Berck-sur-Mer, France
4 Department of Rheumatology, Hôpital Bichat-Claude-Bernard, AP–HP, 46, rue Henri-Huchard, 75018 Paris, France
5 Rheumatology department, Amiens University hospital, Amiens, France
6 Internal Medicine department, Saint-Antoine hospital, AP–HP, Paris, France
7 Sorbonne Université, Institut Pierre Louis d’Épidémiologie et de Santé Publique (iPLESP), UMR S1136, Paris, France
8 AP–HP, Pitié Salpêtrière hospital, Rheumatology department, Paris, France
9 Rheumatology department, Salengro hospital, Lille, France
10 Rheumatology department, Lyon Sud University hospital, Lyon, France
11 Montpellier University, Montpellier, France
12 Internal Medicine department, Bicêtre hospital, AP–HP, France
13 Université Paris-Saclay, Inserm UMR1184 AP–HP, 78, rue du Général-Leclerc, 94275 Le Kremlin, France
14 Rheumatology department, Bordeaux-Pellegrin University hospital, Bordeaux, France
15 Rheumatology department, Saint-Antoine hospital, AP–HP, Paris, France
16 Department of Internal Medicine, Rothschild Hospital Foundation, 29, rue Manin, 75019 Paris, France
17 Hematology department, Rochefort Hospital, Groupe Hospitalier Littoral Atlantique, 1, avenue de Béliron, 17300 Rochefort, France
18 Rheumatology department, Rouen University hospital, Rouen, France
19 Anatomical Pathology Department, Bicêtre Hospital, AP–HP, Le Kremlin-Bicêtre, France

* Corresponding author.
E-mail address: jkedra.pro@gmail.com (J. Kedra)

Accepted 29 March 2022
Available online 28 April 2022