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Circulating T follicular helper cells as emerging biomarkers in pediatric Evans syndrome.

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Evans syndrome remains one of the most challenging diagnoses in pediatric hematology. It is a rare pediatric autoimmune condition with a widely variable clinical course in terms of severity, symptoms, duration of disease, and response to therapies. Pediatric Evans syndrome (pES) also carries significant morbidity due to bleeding and infection. Despite its seemingly simple definition, two contemporaneous or serial immune cytopenias, pES is challenging to diagnose. There is no straightforward clinical test for pES, and distinguishing two immune cytopenias is impeded by significant limitations in serologic testing for both autoimmune thrombocytopenia and neutropenia.[7, 8] Given its diagnostic ambiguity there is a need for reliable biomarkers in pediatric Evans syndrome (pES) to aid in diagnosis and guide clinical management. In this issue of *Haematologica*, Harris et al. [1] characterize circulating CD4+ T follicular helper cells (cTfh) in a large cohort of children with autoimmune cytopenias shedding new light on disease biology and presenting a new diagnostic biomarker for pES.

cTfh cells are the blood counterpart of Tfh cells in the lymphoid tissues. Both cTfh and Tfh cells share expression of CXC-chemokine receptor 5 (CXCR5), ICOS (inducible T cell costimulatory), and programmed cell death protein 1 (PD-1).[2] cTfh cells support B cell activation, facilitate the formation of the germinal center, and drive high affinity antibody production.[2] Beyond promoting normal protective antibody development, cTfh cells may also contribute to pathologic antibody formation. Consistent with this, expansion of cTfh populations have been described in multiple autoimmune conditions including systemic lupus erythematosus, Sjogren syndrome, multiple sclerosis and rheumatoid arthritis, among others.[3, 4]

Smaller studies in pES have previously demonstrated that cTfh cells are increased over those with chronic immune thrombocytopenia (ITP).[5, 6] Harris et al. corroborate these findings in large cohort of 153 children with autoimmune cytopenias including 42 with ES, 85 with ITP and 26 with warm autoimmune hemolytic anemia (wAIHA).

Harris et al. pose that cTfh quantification has clinical utility and can be used to diagnose pES. They report median cTfh percentages of 13% in those with ES as compared to 4.82%, 6.11% and 5.16% in ITP, wAIHA and controls respectively. Furthermore, cTfh cell percentages >9.5% can be used to distinguish pES from ITP or wAIHA with excellent sensitivity (76%) and specificity (86%). Bolstering the clinical relevance of cTfh quantity, cell percentages declined with both treatment and reduced disease activity in those with pES. Comparatively, for individuals with isolated ITP or wAIHA, serial cTfh percentages remained stable within the normal ranges seen in healthy individuals.

Increasingly, hematologists recognized that pES can arise from an ever growing list of monogenic inborn errors of immunity, some of which have targeted therapies and require specific screening for comorbidities.[9, 10] It is even estimated that up to 65% of pES cases are genetically determined.[9] Though rarely performed in adult ES patients, genetic testing is even being incorporated into the upfront diagnostic evaluation of pES.[11] However, the value of genetic testing is less clear when it comes to single lineage cytopenias. Harris et al. extend the relevance of cTfh percentages beyond distinguishing pES itself and demonstrate that cTfh percentages correlate to disease phenotype with higher quantities being linked to co-existing immune disorders and extra-hematologic autoimmune manifestations. Increased cTfh percentages were observed in both ITP and ES patients with associated immune disorders and in ITP patients with co-existing autoimmune features. These findings suggest cTfh quantification

could pinpoint which patients, including those with single lineage cytopenias, would benefit from genetic testing and more comprehensive evaluation for immune disorders.

Beyond, quantification alone, the authors demonstrate that the transcriptional signature of cTfh cells differed markedly between those with active ES, ITP, and wAIHA. Single-cell RNA-sequencing of cTfh cells revealed patients with active, untreated pES exhibited increased T cell activation and a prominent type II interferon (IFN-γ) signature. Consistent with this, plasma cytokine profiling revealed increased CXCL9, a cytokine downstream of IFN-γ signaling, in pES patients compared with controls. In pES, these type II interferon and T cell activation signals diminish with treatment. In contrast, wAIHA patients, regardless of disease activity, despite not having increased cTfh percentages, displayed increased type I interferon (IFN-α/β) signatures and on hierarchical clustering grouped more closely to those with active ES. In contrast, ITP patients lacked strong interferon-driven activation signatures and exhibited reduced evidence of T cell activation. Collectively, Harris et al. not only point to cTfh transcriptional profiles as a tool for distinguishing ES, wAIHA and ITP, but importantly highlight type I and II IFN pathways as promising therapeutic targets in ES and wAIHA.

While continued validation work on cTfh percentages and immune signatures in pediatric immune cytopenias is needed, this paper offers a compelling step towards bringing diagnostic clarity to a disorder long marked by unknowns and advances our understanding of pES pathogenesis.

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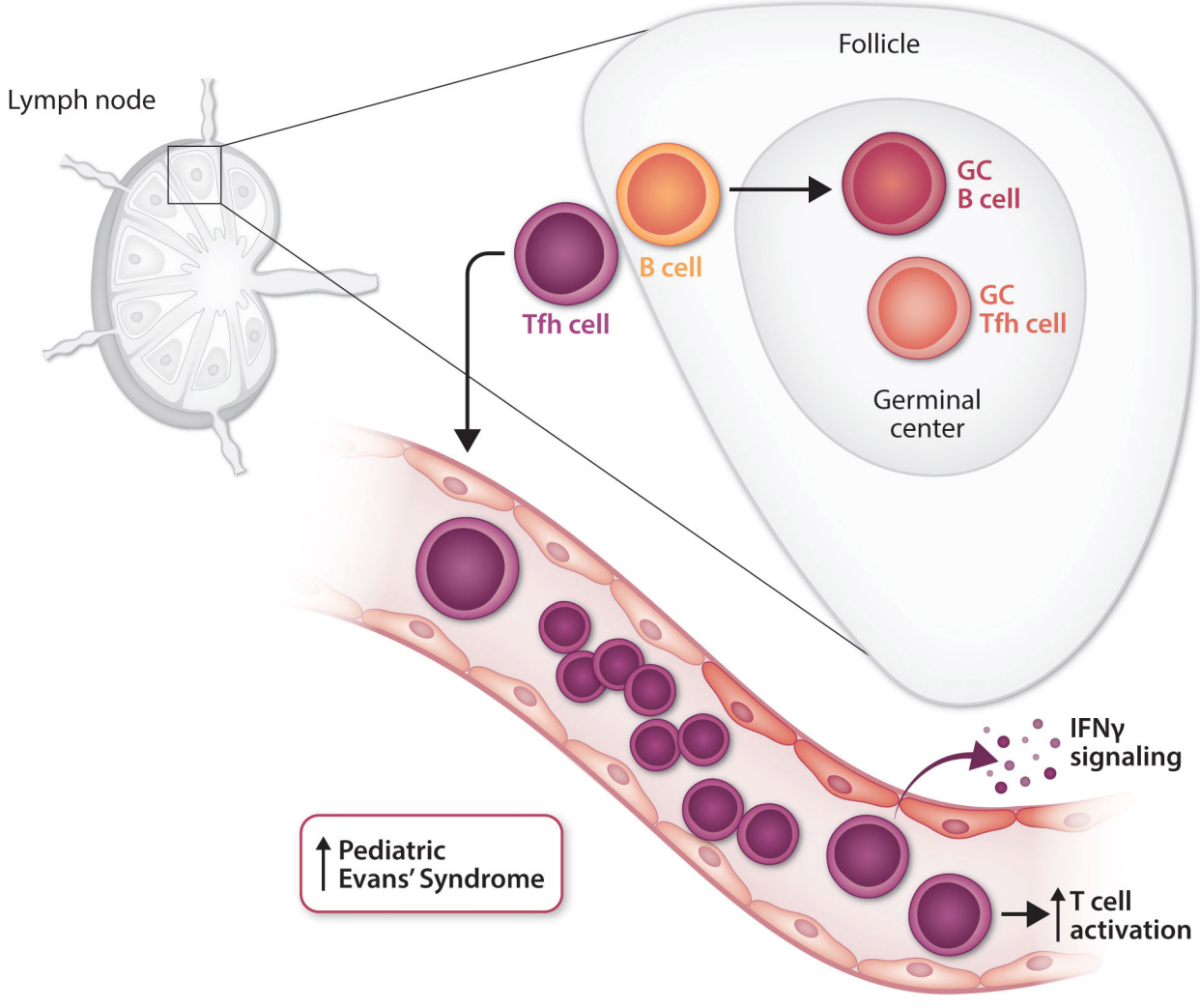
Figure legend

Schematic model to understand elevated circulating CD4+ T follicular helper cells (cTfh) in pediatric Evans Syndrome (pES). cTfh cells are the blood counterpart of Tfh cells in the lymphoid tissues. Both cTfh and Tfh cells share expression of CXC-chemokine receptor 5 (CXCR5), ICOS (inducible T cell costimulatory), and programmed cell death protein 1 (PD-1). While not typically quantified in standard clinical panels, cTfh would be identified as CD4+CXCR5+ cells by flow cytometric testing. These cells support B cell activation, facilitate the formation of lymph node germinal centers, and drive high affinity antibody production. Beyond promoting normal protective antibody development, cTfh also contribute to pathologic antibody formation. Harris et al. pose that cTfh may be released into the circulation from lymph nodes causing their increased numbers and elevated plasma interferon-gamma (IFN-γ) signatures leading to autoreactive T cell activation. They propose that peripheral blood quantification of cTfh has clinical utility and can be used to diagnose pES.


Lymph node
Follicle
GC
B cell
B cell
GC
Tfh cell
Tfh cell
Germinal
center
IFNγ
signaling
Pediatric
Evans' Syndrome
T cell
activation