Defining B-cell defects and correlation with complications in patients with common variable immune deficiency

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The interesting article in this issue entitled “Defects in memory B-cell and plasma cell subsets expressing different immunoglobulin subclasses in patients with CVID and immunoglobulin subclass deficiencies” from the EuroFlow group led by Jacques van Dongen, updates the EUROclass classification and confirms and extends an earlier study from the group, which was previously in Rotterdam and now in Leiden. Use of an extended panel of mAbs to define 41 circulating B-cell and plasma cell subsets adds to our knowledge of the differing B-cell abnormalities in patients with selective IgA deficiencies (SIgADs) and those with common variable immunodeficiency disorders (CVIDs). CVIDs are heterogeneous, with different peripheral B-cell findings and also varying clinical complications and outcomes that lead to different but largely nonoverlapping clinical phenotypes. SIgADs are also varied in clinical presentations, complications, and familial inheritance. Flow cytometry is standard for the diagnosis of predominantly antibody deficiencies (PADs), the diagnosis for patients in whom production of protective antibodies has failed because of an intrinsic immune defect. The advice in this article regarding which mAbs to use and how to mix them to gain maximum information is helpful; their previous publication used the same excellent methodology. However, extensive use of mAbs and complex analytic programs makes this rather tricky and expensive for routine diagnostic use at present (Table I).

This method finds sufficient B cells to classify the type of PAD in patients with less than 1% B cells, who are normally excluded from CVIDs. Here the authors were able to identify sufficient B cells in all patients with “CVID” because of the use of the method for detection of minimal residual disease in multiple myeloma. Not only important for PADs, this method will also be useful in dissecting secondary antibody failures and might help lead to those patients needing long-term therapeutic immunoglobulin and those who will recover antibody production in due course (Table I).

The purpose of this research was to delineate the varied defects in antibody production. Blood samples from 139 patients, 61 with CVID, 68 with SIgAD, and 10 with IgG subclass deficiencies with IgA deficiency, were tested, along with those from 223 age-matched control subjects. The importance of using age-matched control subjects is emphasized in the article because many diagnostic laboratories still use adult levels of B-cell subpopulations for comparisons with their patients. Overall decreased IgA1- and/or IgA2- plasma cell counts were found in all patients, except for 2 patients with SlgAD who showed abnormally reduced numbers of surface membrane IgA1- and IgA2- memory B cells, confirming the failure of IgA production, which is in line with severely reduced serum IgA levels. The authors defined 2 subgroups of patients with SlgAD: those with mild reductions in numbers of surface membrane IgA- memory B cells and those with severely reduced numbers of surface membrane IgA- memory B cells. Correlations with clinical findings noted that the latter group had greater frequencies of non–respiratory tract infections and autoimmunity and had affected family members. This will be helpful to clinicians in distinguishing patients at diagnosis who are likely to remain well from those with potential complications.

Overall, the decreased total of plasma cells and/or immunoglobulin heavy chain switched plasma cells in peripheral blood was confirmed as a hallmark of CVID, which is in line with previous bone marrow and lymph node findings. Driessen et al found 5 B-cell patterns with different blocks in B-cell production, which reflected immunologically homogenous patient groups. These ranged from an early B-cell production defect in a few patients through defects in early peripheral B-cell maturation or survival, defects in B-cell activation and proliferation, and failure of germinal center development to post–germinal center defects. The present study, which has many more patients and a 3-fold increase in healthy control subjects to enable age matching, resulted in 6 CVID groups along the same lines, with data from several European groups.

This methodology is good for dissecting the various mechanisms of antibody failure and might prove useful in matching defects in antibody production pathways with any proposed potential PAD-related genes in data from next-generation sequencing. However, the roles of genetic variants are at best unclear in patients with sporadic adult-onset CVIDs. In this report there are good correlations between clinical complications and the 6 clusters of patients with CVID. The high prevalence of infections, bronchiectasis, and splenomegaly in most patients with CVID is not surprising (as found in other studies). The group 4 CVID cluster includes patients with cytopenias, enteropathy, and systemic autoimmunity; this might suggest an autoimmune cause for CVID enteropathies that is worthy exploring. The increase of granulomata in cluster 6 (and to some extent in cluster 3) could help lead to a T-cell defect in this group when T-cell populations are dissected in a similar fashion. In contrast, the lack of granuloma in patient clusters 1, 4, and 5...
TABLE I. Key points

- Extends earlier EuroFlow methodology to find more clinically relevant homogeneous subgroups of patients with SlgADs or CVIDs by analyzing B-cell subpopulations and comparing with age-matched healthy control subjects
- Divides SlgADs into 2 distinct groups with different clinical implications
- Divides CVIDs into 6 distinct groups that correlate with clinical phenotypes/complications
- Might prove useful in matching defects in antibody production pathways with proposed potential PAD-related genes in data from next-generation sequencing in the future
- Methodology could be important in dissecting secondary antibody failures and in distinguishing those patients needing long-term therapeutic immunoglobulin and those who will recover antibody production in due course
- Extensive use of mAbs and complex analytic programs makes this rather difficult and expensive for routine diagnostic use

might indicate that the cause of granulomata is quite different from that of other disease-related complications.3

This elegant methodology is the first to correlate in vitro assays with clinical phenotypes. This article becomes an invaluable tool if it can provide tools to identify patients at high risk of complications when they present. However, it is important to determine whether there are any changes in the patient cohort with time or therapy to ensure that these features are not a result of a particular complication or the treatment administered for that complication. Despite extensive efforts, monogenic alterations responsible for any primary antibody deficiency are detected rarely, and it is likely that several genetic variants contribute to antibody failure,9 whereas other genes contribute to complications in the various CVID phenotypes. Furthermore, the distinction between pure B-cell failure and combined immune deficiencies is tricky,10,11 and many patients are mislabeled as having CVID rather than a more appropriate diagnosis of combined immune deficiency, making the relevance of a particular newfound genetic variant even more confusing. Comparison with known monogenic conditions, particularly those in which antibody failure is associated with non-B-cell defects, might help shed light on these complex mechanisms.

The data in this EuroFlow article increases the likelihood that there are several gene defects/variants among patients with CVID. Clinical phenotypes are still broad and do not provide mechanisms in this polygenic group of conditions.4 To determine the role of such genetic variants, the clinical phenotypes/complications and B cell immunotypes need to be matched, along with clinical outcomes, so that understanding of CVIDs and the related PADs and their mechanisms can be unraveled to provide patients and clinicians with prognoses in the future (Table I).

Therefore the final question is this: Does classifying heterogeneous diseases with antibody failure by using flow cytometry help in terms of diagnosis and prognosis? It might, if genes related to different stages of B-cell development are linked to genes responsible for disease-related complications, but this might not be the case. Complications might depend on genetic influences of immune dysregulation, particular pathogen susceptibility, or the potential for autoimmunity or lymphoid malignancies, all of which can affect patients with CVIDs.

Classification of PADS is tricky at best. Although the authors of this article have attempted to correlate their findings with the European Society for Immunodeficiencies and International Union of Immunological Societies classifications of PADS, this might not be a helpful avenue to pursue when trying to determine underlying mechanisms in primary antibody deficiencies because the 2 different categorizations are used for different reasons in different countries. Until long-term patient data are available and flow cytometric studies in different centers use the same protocols (as shown in this study), teasing out the scientific basis for primary antibody failure will remain difficult for these comparatively rare but heterogeneous diseases.

REFERENCES