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EDITORIAL

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Diagnostic Management of Chronic Granulomatous Disease

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Chronic granulomatous disease (CGD), one of the neutrophil function disorders, often presents with recurrent skin or deep organ abscess and respiratory infections. Although X-linked CGD (X CGD) is prevalent in the western world, autosomal recessive forms (p22phox, p47phox and p67phox defects) are mostly seen in Middle East regions with high consanguinity rates (1). Recently, dihydrorhodamine-1,2,3 (DHR) assay by flow cytometry has been used instead of Nitroblue tetrazolium test (NBT) that needs microscopic evaluation. The differential diagnosis of CGD is crucial for severe infections, especially with opportunistic pathogens in intensive care units. The diagnostic process of CGD is a problem for many clinicians due to the availability of neutrophil function tests. However, clinical and immunological experience are essential to catch CGD case. Parental consanguinity, sibling death history and increased IgG level are the major questions to be answered. In recent years, many centers access to reference laboratories for diagnosing or confirming their results by blood sample shipping services. Phagocytic disorders should be checked in cases of recurrent infectious diseases, invasive fungal diseases, opportunistic pathogens, Bacille de Calmette Guerin (BCG) vaccine related complications, unexplained lymphadenitis or osteomyelitis, and chronic inflammatory disorders (2). If any family members have CGD, BCG vaccination should be postponed until the sibling's CGD suspicion is excluded by DHR test. Clinicians may also identify CGD together with other rare diseases like CVID with hypogammaglobulinemia and Kabuki syndrome (1,3,4).

In general, X-CGD patients and AR-CGD patients with p22phox or p67phox defect have very low oxidase activity 1% and severe clinical presentation. CGD is mostly diagnosed in the childhood period but due to the development of diagnostic facilities and the awareness of clinicians, some patients with residual oxidase activity have been diagnosed at older ages in the second or third decades (1,5,6). Most of lately diagnosed CGD patients have p47phox deficiency with 5-7% residual oxidase activity (1,3,4). Experienced clinical evaluation, familial history and laboratory tests such as the DHR assay may also help to identify the asymptomatic patients. Residual oxidase activity may postpone the clinical presentation but it is not sufficient for recovery from severe infections, without clinical support (7). Most of the patients with residual oxidase activity have a hotspot mutation in exon 2 of NCF1 gene (p47phox). Additionally, a few patients with hypomorphic mutation in CYBA (p22phox) gene, NCF2 (p67phox) gene and X-CGD form were also described previously with residual oxidase activity (1, 8). The laboratory diagnosis of CGD may needs additional confirmation, especially in older ages and when neutrophils have residual oxidase activity (9).

Bone morrow transplantation is a curative therapy for CGD. Before transplantation, DHR test should be done for checking healthy neutrophils in donor. It may also be useful for the follow-up after transplantation for chimera of neutrophils in transplanted patient. The DHR assay, besides being a rapid and sensitive assay for the diagnosis of CGD, it also provides clues on X-CGD and AR-CGD differen-

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tiation by shoving a bimodal neutrophil group specific for female carriers of X-CGD (9). Furthermore, X-CGD carrier may need to be followed up by DHR assay for skewing of lyonization. In normal way, both X-chromosome randomly inactivated 50% of each, in carrier (10). A severe clinical manifestation of symptoms in carriers of X-CGD may occur If lyonization is non-randomly skewed to diseased-X-ch (11). Patient with complete myeloperoxidase (cMPO) deficiency can cause a similar result with CGD in the DHR assay. So, MPO expression should be checked by flow cytometry for the exclusion of MPO deficiency (12). In conclusion, it should be noted that PIDs show heterogeneous manifestations and therefore require a multidisciplinary perspective to recognizing clues in patients with uncommon symptoms.

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