

## ACQUIRED CHRONIC NEUTROPENIA

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Over the past decade new data have been discovered regarding both the physiopathological and the clinical aspects of acquired chronic neutropenia, some of which are worth examining.

The autoimmune neutropenia of infancy syndrome was well defined by Lalezari et al. in 1986.<sup>1</sup> Neutrophil antibodies were demonstrated in 119 of 121 cases of chronic neutropenia by a combination of immunofluorescence and agglutination tests. The median age of patients at diagnosis was 8 months, with a female/male ratio of 6:4. Neutropenia was severe, selective, usually associated with monocytosis and eosinophilia. Bone marrow showed myeloid hyperplasia and reduced mature neutrophils. Patients who presented recurrent fever and infection were treated with antibiotics and occasionally with intravenous immunoglobulins. Spontaneous cure appeared to be the rule, after a median disease duration of 20 months.

Small series of adult patients with unexplained neutropenia (chronic idiopathic neutropenia) were described by Dale et al. in 1979,<sup>2</sup> and by Kyle and Linman<sup>3</sup> and Greenberg et al.<sup>4</sup> in 1980. Most patients were female; there was no evidence of drug intake or other pathologic conditions and bone marrow was normal. Follow-up failed to evidence either the development of another hematologic disease or an initially occult primary etiology. An immune mechanism for the neutropenia was suggested in a subset of patients. Antineutrophil antibodies were found in 3 out of 19 patients in Greenberg's series. More recently, Logue et al.<sup>5</sup> detected antineutrophil antibodies in the sera of 36% of 121 adult patients with chronic idiopathic neutropenia. In a subgroup of these patients neutropenia was combined with anemia and/or thrombocytopenia.

The cause of chronic neutropenia in which

antineutrophil antibodies are absent is unknown. Bone marrow myeloid progenitor numbers are usually normal. The response of some patients to therapy with G-CSF<sup>6,7</sup> suggests a possible etiologic role for this growth factor, i.e. relative or absolute deficiency in its production, a low number of receptors on neutrophil precursors, slight binding affinity for the protein. The recent interesting observation of deficient G-CSF production by mononuclear cells from a patient with chronic idiopathic neutropenia, in spite of an adequate accumulation of G-CSF mRNA, suggests that the defect in endogenous G-CSF production at the post-transcriptional level may also be an etiological factor.<sup>8</sup> On the contrary, GM-CSF does not seem to play a role in the pathogenesis of chronic idiopathic neutropenia, since it has been unsuccessful in the treatment of this condition.<sup>9</sup>

Autoimmune neutropenia may occur alone, or together with other autoimmune or connective tissue disorders. The T- $\gamma$  lymphocytosis syndrome is usually linked with severe immune neutropenia;<sup>10</sup> moreover, an association between autoimmune neutropenia and bone marrow transplantation have been reported in some cases.<sup>11</sup>

Antibodies against neutrophils or CFU-GM and immune complexes may be found in autoimmune neutropenia. Notwithstanding many technical difficulties, various methods have been developed for detecting antineutrophil antibodies, including agglutination and microagglutination, cytotoxicity, direct and indirect immunofluorescence, direct and indirect antiglobulin assays, and tests involving the binding of staphylococcal protein A to immunoglobulins on the surface of cells.

An updated review of the role and nature of autoantibodies to neutrophils in primary and

secondary autoimmune neutropenia was recently published by Shastri and Logue.<sup>12</sup> The maturational specificity of antineutrophil antibodies has been related to the severity of neutropenia; antibodies that bind to immature myeloid cells were associated with the most severe forms.<sup>13</sup> Very little is known about the antigenic specificities of naturally occurring antineutrophil autoantibodies. In a subset of patients with neutropenia and antineutrophil antibodies, Hartman et al. detected specific IgG binding to a 43-Kd neutrophil membrane-associated protein, which was identified as actin.<sup>14</sup> Some patients with autoimmune neutropenia have autoantibodies specific for the functionally important neutrophil adhesion proteins CD11b/CD18.<sup>15</sup> These autoantibodies may, in some cases, interfere with neutrophil function, thereby amplifying the risk of infection associated with neutropenia. Recently the neutrophil antigens NA1 and NA2 were identified as glycosylated isoforms of neutrophil Fc  $\gamma$  receptor III,<sup>16</sup> and the NB1 antigen was shown to reside on a 58- to 64-Kd glycoprotein present on the surface of neutrophils and in secondary granules.<sup>17</sup>

Although the physiopathological significance of this immune dysregulation is not fully clear, events such as phagocytosis of sensitized neutrophils, complement-fixing of antineutrophil antibodies and binding of immune complexes to neutrophil Fc or complement receptors may be important mechanisms for neutropenia and decreased neutrophil function.

Patients with chronic idiopathic or autoimmune neutropenia suffer from intermittent infections; in general, symptoms are mild and include malaise, pharyngitis, cellulitis, mucosal ulcerations and periodontal disease. The goal of therapy is to prevent recurrent infections and not necessarily to increase neutrophil counts. Therefore symptomatic or prophylactic treatment with antibiotics is the mainstay of therapy, especially in children, for whom spontaneous cure is the rule. Infections, however, are less frequent in autoimmune neutropenia than in secondary neutropenias of similar severity, and are usually not life-threatening.

Traditional modalities of treatment in adults include corticosteroids and cytotoxic drugs. Corticosteroids, administered according to different schedules, have been used with success in some cases. Their potential mechanisms of

action include reticuloendothelial blockade and decreased antibody production.<sup>18</sup> Among the cytotoxic agents cyclophosphamide and methotrexate have proven efficacious. Methotrexate was also employed successfully in patients with Felty's syndrome.<sup>19</sup>

Intravenous immunoglobulins are useful in both children and adults; they are the treatment of choice in cases of active infection. In fact, they induce a short but rapid response that allows successful treatment of infections.<sup>20-22</sup> Possible mechanisms of action are transitory reticuloendothelial blockade and probable anti-idiotypic suppression of autoantibodies.

The utilization of hematopoietic growth factors is more recent. These substances support the proliferation and terminal differentiation of myeloid progenitor cells and enhance granulocyte functions. Although only sporadic cases have been reported, the initial results seem encouraging.<sup>23-24</sup> In view of the short-term response they elicit, this treatment is most effective in patients with active systemic infection or in those undergoing major surgery.

In isolated cases of Felty's syndrome and chronic idiopathic neutropenia,<sup>25</sup> plasmapheresis has been used with positive results, while the role of splenectomy in autoimmune neutropenia is ill-defined and a beneficial effect of lithium carbonate is questionable.

In patients refractory to the above-reported modalities of treatment, cyclosporin A may be indicated, as suggested by Martino et al. in this issue of *Haematologica*. This immunomodulating drug has been previously used with good results in cyclic neutropenia,<sup>26</sup> Felty's syndrome<sup>27</sup> and T- $\gamma$  lymphocytosis,<sup>28,29</sup> as well as in other immunologic cytopenias such as pure red cell aplasia and aplastic anemia. Its mechanisms of action include inhibition of cellular immune reactions and reduction of immunoglobulin synthesis. Although further confirmation is required, its role in the treatment of autoimmune neutropenia seems promising.

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## References

1. Lalezari P, Khorshidi M, Petrosova M. Autoimmune neutropenia of infancy. *J Pediatr* 1986; 109:764-9.
2. Kyle R. Natural history of chronic idiopathic neutropenia. *N Engl J Med* 1980; 302:908-9.
3. Dale D, Guerry D, Weewrka J, Bull J, Chusid M. Chronic neutropenia. *Medicine* 1979; 58:128-44.
4. Greenberg P, Mara B, Steed S, Boxer L. The chronic idio-

- pathic neutropenia syndrome. Correlation of clinical features with in vitro parameters of granulopoiesis. *Blood* 1980; 55:915-24.
5. Logue GL, Shastri KA, Laughlin M, Shimm DS, Ziolkowski LM, Iglehart JL. Idiopathic neutropenia: antineutrophil antibodies and clinical correlations. *Am J Med* 1991; 90:211-6.
  6. Jakubowski AA, Souza L, Kelly F, et al. Effects of human granulocyte colony-stimulating factor in a patient with idiopathic neutropenia. *N Engl J Med* 1989; 320:38-42.
  7. Furukawa T, Takahashi M, Moriyama Y, Koike T, Kurokawa I, Shibata A. Successful treatment of chronic idiopathic neutropenia using recombinant granulocyte colony-stimulating factor. *Ann Hematol* 1991; 62:22-4.
  8. Morikawa K, Yamamori S, Oiwa K, et al. Impaired G-CSF production at post-transcriptional level in a patient with chronic idiopathic neutropenia. *Br J Haematol* 1993; 85:200-2.
  9. Wodzinski M, Hampton KK, Reilly JT. Differential effect of G-CSF and GM-CSF in acquired chronic neutropenia. *Br J Haematol* 1991; 77:249-50.
  10. Rustagi PK, Han T, Ziolkowski L, Farolino DL, Currie MS, Logue GL. Granulocyte antibodies in leukemic chronic lymphoproliferative disorders. *Br J Haematol* 1987; 66:461-5.
  11. Klumpp TR. Antibody-mediated neutropenia following bone marrow transplantation. *Int J Clin Lab Res* 1993; 23:4-8.
  12. Shastri KA, Logue GL. Autoimmune neutropenia. *Blood* 1993; 81:1984-95.
  13. Levitt LJ, Ries CA, Greenberg PA. Pure white cell aplasia. Antibody mediated autoimmune inhibition of granulopoiesis. *N Engl J Med* 1983; 308:1141-6.
  14. Hartman KR, Mallet MK, Nath J, Wright DG. Antibodies to actin in autoimmune neutropenia. *Blood* 1990; 75:736-43.
  15. Hartman KR, Wright DG. Identification of autoantibodies specific for the neutrophil adhesion glycoproteins CD11b/CD18 in patients with autoimmune neutropenia. *Blood* 1991; 78:1096-104.
  16. Ory PA, Clark MR, Kwok EE, Clarkson SB, Goldstein IM. Sequences of complementary DNAs that encode the NA1 and NA2 forms of Fc receptor III on human neutrophils. *J Clin Invest* 1989; 84:1688-91.
  17. Stronceck DF, Skubitz KM, Shanker RA, Mendiola JR, McCullough JJ. Biochemical characterization of the neutrophil specific antigen NB1. *Blood* 1990; 75:744-55.
  18. Cines DB, Passero F, Guerry D, Bina M, Dusak B, Schreider A. Granulocyte associated IgG in neutropenic disorders. *Blood* 1982; 59:124-32.
  19. Fiechtner JJ, Miller DR, Starkebaum G. Reversal of neutropenia with methotrexate treatment in patients with Felty's syndrome. *Arthritis Rheum* 1989; 32:194-201.
  20. Bussel J, Lalezari P, Hilgartner P, et al. Reversal of neutropenia with intravenous gammaglobulin in autoimmune neutropenia of infancy. *Blood* 1983; 62:398-400.
  21. Breedveld FC, Brand A, van Aken WF. High dose intravenous gammaglobulin for Felty's syndrome. *J Rheumatol* 1985; 12:700-2.
  22. Favareto F, Molinari AC, Arigliani R, Strada P, Reali G, Mori PG. Immunoglobulin therapy in childhood immune neutropenia. *Haematologica* 1987; 72:473-4.
  23. Ganser A, Ottmann OG, Erdmann H, Schulz G, Hoelzer D. The effect of recombinant human granulocyte-macrophage colony stimulating factor on neutropenia and related morbidity in chronic severe neutropenia. *Ann Intern Med* 1989; 111:887-92.
  24. Takahashi K, Taniguchi S, Akashi K et al. Human recombinant granulocyte colony-stimulating factor for the treatment of autoimmune neutropenia. *Acta Haematol* 1991; 86:95-8.
  25. Selleri C, Catalano L, Alfinito F, De Rosa G, Vaglio S, Rotoli B. Cyclosporin A in adult-onset cyclic neutropenia. *Br J Haematol* 1988; 68:137-41.
  26. Canvin JMG, Dalal BI, Baragar F, Johnston JB. Cyclosporin for the treatment of granulocytopenia in Felty's syndrome. *Am J Hematol* 1991; 36:219-20.
  27. Pastor E, Sayas MJ. Severe neutropenia associated with large granular lymphocyte lymphocytosis: successful control with cyclosporin A. *Blut* 1989; 59:501-2.
  28. Garapidou V, Tsatalas C, Sinacos Z. Severe neutropenia in a patient with large granular lymphocytosis: prolonged successful control with cyclosporin A. *Haematologica* 1991; 76:424-5.
  29. Caligaris-Cappio F, Camussi G, Gavosto F. Idiopathic neutropenia with normocellular bone marrow: an immune-complex disease. *Br J Haematol* 1979; 43:595-605.