CASE REPORT

An infant with chronic severe neutropenia

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SUMMARY

Neutropenia in infancy and childhood poses a diagnostic challenge as the aetiology ranges from acute life-threatening conditions to chronic benign diseases. Chronic benign neutropenia of infancy is a rare disorder occurring in 1:100 000. The neutrophil count continues to be low for a prolonged period until spontaneous resolution by the age of 3–4 years. Such infants are having higher incidences of minor infections requiring treatment with antibiotics and rare incidences of meningitis and sepsis. The authors describe an infant presenting with fever and cervical lymphadenitis, who was found to have isolated severe neutropenia and its persistence posing a diagnostic challenge. The prolonged course with minor infections and absence of serious underlying conditions finally confirmed chronic benign neutropenia of infancy.

BACKGROUND

Neutropenia is defined as a decrease in the circulating or absolute neutrophil count (ANC) to less than $1500/\text{mm}^3$ and considered severe when ANC is less than $500/\text{mm}^3$.^{1–2} Aetiologies of neutropenia include transient conditions, serious disorders and chronic diseases. Neutropenia in infancy/childhood may present as acute life-threatening disease or run a benign course with minor infections. Chronic benign neutropenia (CBN) is a rare clinical situation of autoimmune aetiology that results in low ANC below $500/\text{mm}^3$ for over a 3–6-month period.^{1–4} Apart from higher incidences of minor infections, meningitis and sepsis have been rarely reported with CBN.² We describe acute severe neutropenia transitioning to chronic neutropenia in an infant and its course over a prolonged period with minor infections.

CASE PRESENTATION

An 11-month-old male infant presented with fever and cough of 2 days duration. He was prescribed amoxicillin for acute pharyngitis on an outpatient basis. He returned after 4 days with persisting moderate degree of fever and cough. On examination, he had fever of 102°F , pulse of 130/min and a respiratory rate of 22/min. His throat was congested with whitish patches. Rest of the general examination and systemic examinations were normal. His history revealed birth at a full term by vaginal route and normal growth and development. He had been immunised with Bacillus Calmette-Guérin and three doses each of diphtheria, tetanus, pertussis/oral polio vaccine, *Haemophilus influenza* vaccine and hepatitis B vaccine. Complete blood counts (CBC) were ordered in view of continued fever.

INVESTIGATIONS

CBC revealed a haemoglobin (Hb) of 11.6 g/dL , a platelet count of $324\,000/\text{mm}^3$ and a total leucocyte count (TLC) of $11\,300/\text{mm}^3$ with neutrophils 2% (ANC of $226/\text{mm}^3$), lymphocytes 40%, monocytes 14% and eosinophils 44%. Red blood cells were normocytic and normochromic. Owing to severe neutropenia he was hospitalised and intravenous antibiotics were started after sending blood for culture. He became afebrile by 36 h.

By 48 h, a swelling was noticed in the left upper cervical region with recurrence of fever. The swelling gradually increased in size ($4\text{ cm}\times 3\text{ cm}$) and was tender. Left cervical lymphadenopathy was diagnosed and an ultrasonography of the swelling confirmed the same. Repeat TLC was $5500/\text{mm}^3$ and ANC, 220. Two days later ANC dropped to 134. Serum IgG, IgA, IgM and IgE levels were normal. Tests for secondary immunodeficiency were negative. Nitroblue tetrazolium test showed phagocytosis in occasional neutrophils. Blood culture remained sterile at 72 h. Ultrasonography of the abdomen was normal. Fever and left cervical lymphadenopathy decreased over 5 days. Repeat CBC revealed a TLC of $6000/\text{mm}^3$, with neutrophils 4% (ANC, 240), lymphocytes 73%, monocytes 17%, eosinophils 5% and basophils 1%. For persistent neutropenia, bone marrow study was performed. Bone marrow aspirate showed myeloid hyperplasia with increased precursor cells, reduced mature neutrophils, normal erythropoiesis, normal megakaryocytes and no abnormal cells. The M:E ratio was 7:1.

TREATMENT

With intravenous antibiotics (amoxicillin clavulanate) he continued to have low-grade fever and mild induration at the bone marrow aspiration site on day 14. The ANC remained at $240/\text{mm}^3$ and hence three doses of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was given ($5\text{ }\mu\text{g/kg}$ body weight). The ANC improved to $3920/\text{mm}^3$ and the boy was asymptomatic. By 4 days following discontinuation of rhG-CSF therapy, ANC dropped again to 252. He was discharged on trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis. Two weeks later he was given prednisolone and on prednisolone therapy he maintained an ANC of between 546 and $736/\text{mm}^3$. After 4 weeks, steroids were stopped and he was followed up biweekly and subsequently at monthly intervals. His ANC remained in the range of $110\text{--}264/\text{mm}^3$.

OUTCOME AND FOLLOW-UP

At 6 months follow-up, his TLC was $5800/\text{mm}^3$ with neutrophils 1% (ANC, 58) lymphocytes 69%,

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monocytes 7% and eosinophils 23%, Hb 13 g% and platelets 196 000/mm³. He had two episodes of upper respiratory tract infections which were managed on outpatient basis. At 1-year follow-up his ANC was 264/mm³. Except for a couple of upper respiratory tract infections, which were treated with oral antibiotics the child did not have any serious infections. His growth and development were normal.

DISCUSSION

A severe neutropenia associated with respiratory tract infection and left cervical lymphadenopathy in an infant posed a diagnostic challenge. Its persistence on serial monitoring has lead to bone marrow examination and workup for immunodeficiency. Bone marrow examination ruled out serious underlying conditions. The benign nature and persistent low neutrophil count over a period of 6 months confirmed the diagnosis of CBN.

CBN, also called as primary autoimmune neutropenia, is a rare condition in which neutropenia, the sole haematological abnormality, persists for a longer period. At the onset because of low ANC it may lead to diagnostic challenge. CBN appears predominantly (90%) in infancy¹ as in the present case. Onset may be as early as 6–12 months of age with equal frequency in boys and girls.² The clinical course is variable ranging from detection with life-threatening infections to incidental discovery. Infants and children with CBN have frequent minor infections including cellulitis, mucositis, gingivitis, ear infections, pharyngitis, diarrhoea and pneumonia. Common and sometimes serious infections around the genital or rectal area may occur in little girls. Meningitis and sepsis also have been reported rarely.^{2–5} Gram-positive bacteria especially *Staphylococcus aureus* are the most common offending microorganisms. Infections with Gram-negative organisms such as *Pseudomonas aeruginosa* may also occur. Infections decrease with age with an ANC of more than 400/mm³. Sometimes, neutropenia may only be an incidental finding when the child is taken to the paediatrician for a general check-up. The child usually appears healthy with no abnormal findings on physical examination.

The laboratory findings of CBN include either normal or slightly decreased TLC. The ANC usually fluctuates between 0 and 500/mm³. Peripheral monocytosis and eosinophilia may be associated. The rest of the blood count is normal. Presence of antineutrophil autoantibody favours the diagnosis^{4–5} although they are not always detectable.^{2–3} Only 21% of the 19 children with CBN had positive antineutrophil antibodies in one series.³ Bone marrow usually shows myeloid hyperplasia with maturational arrest of neutrophils particularly at late stages of development. In the present case, TLC was normal, ANC was always below 500/mm³, peripheral smear showed monocytosis and eosinophilia and bone marrow showed myeloid hyperplasia.

Symptomatic treatment of infections with antibiotics is the first line of treatment in infants with CBN. rhG-CSF is useful in temporarily increasing the neutrophil (100%) count during severe infection or before surgery.¹ An increase in ANC occurs following 1–2 days of starting therapy. However, the elevations of ANC is transient and the neutrophil count drops once the therapy is stopped.^{3–5} Long-term low-dose therapy with dosages ranging from 1 to 5 µg/kg twice weekly has been tried by many authors.^{2–5} Administration of rhG-CSF resulting in resolution of

all pre-existing chronic infections, reduction in the frequency of new infectious episodes and discontinuation of prophylactic antibiotics has been reported.⁵ In the present case, normalisation of ANC was observed with rhG-CSF therapy. Corticosteroids and intravenous immunoglobulin (IVIG) have also been used to increase neutrophils with success rates of 75% and 50%, respectively.² We observed a mild elevation in ANC with steroid therapy. Usefulness of TMP-SMX until the resolution of neutropenia in reducing the incidence of infection with no adverse effects has been reported.⁶ We also observed this effect while the infant was on TMP-SMX prophylaxis.

Therapeutic approaches, including prophylactic antibiotics, IVIG, steroids and rhG-CSF should be reserved for infants with frequent or severe infections rather than to treat a specific neutrophil value. In most (95%) cases of CBN of childhood spontaneous remission would be observed within 24 months of diagnosis.^{1–5} In conclusion, CBN of infancy/childhood is a rare condition whose diagnosis is based on blood counts. It poses an initial diagnosis challenge and subsequently follows a chronic and benign course. With proper investigative protocol and antibiotic treatment, children usually outgrow their disease.

Learning points

- ▶ Neutropenia in infancy and childhood poses a diagnostic challenge.
- ▶ Aetiology may vary from benign conditions to serious life-threatening conditions.
- ▶ An infant with severe neutropenia requires a careful workup for the underlying conditions.
- ▶ Chronic benign neutropenia of infancy can only be diagnosed after a careful follow-up over a period of time.

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