

CASE STUDY

A 13-YEAR-OLD HIV-INFECTED GIRL WITH THROMBOCYTOPENIA

Paediatric case discussion, July 2006

Southern African HIV Clinicians Society: Paediatric Internet-based Discussion Group (PDG)

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The Paediatric Internet-based Discussion Group (PDG) assists health care professionals to resolve HIV-related clinical problems through the use of case studies. Difficult and interesting cases are e-mailed to group members, who e-mail their responses to all participants. This forum allows users to consult with one another, share their experiences, and utilise one another's expertise of treatment of HIV and HIV-related illnesses in an online discussion. The following case was presented to a group of South African paediatricians. The opinions of the participants are outlined below, followed by recommendations from experts in the field. *Readers should be aware that opinions vary and may depend on resources available and regional differences in standard of care. Clinical judgement, reinforced by data, is of paramount importance.*

THE CASE

A 13-year-old girl is known to have been HIV infected since 4 years of age. Her weight was 56 kg, her height 172 cm and her body surface area (BSA) 1.52 m² (on 10 November 2005). Her mental and physical growth have been normal so far. Her latest CD4 count was 727 cells/ μ l (32%) and her viral load is 41 652 copies/ml. Her latest full blood count (FBC) reveals a white blood cell count of $5.9 \times 10^9/l$, a haemoglobin concentration of 8.32 g/dl, a mean corpuscular volume (MCV) of 72.40, and a platelet count of $3.0 \times 10^9/l$. Her maximum platelet count in the past year was $2.1 \times 10^9/l$. The aspartate aminotransferase (AST) value was 23 and the alanine aminotransferase (ALT) value 13.

The patient was referred by an ENT surgeon with recurrent epistaxis. She has received several transfusions of platelets and blood over several admissions in the past. She had been on prednisolone on and off for the past year or so. BMA was done in December 2005: iron deficiency was present, and megakaryocytes were abundant. She started her menses recently, and has experienced heavy and prolonged bleeding. She is on iron supplements and prednisolone. Gynaecologists noted clots on vaginal examination and felt that her bleeding could be arrested with tranexamic acid and some hormonal treatment.

THE QUESTIONS PARTICIPANTS WERE ASKED TO CONSIDER:

1. What is causing the patient's persistently low platelets?
2. Why has there been no response of her thrombocytopenia to prednisolone?
3. What other treatment options are available for her thrombocytopenia?
4. At what stage is her HIV infection?
5. Is she eligible for antiretroviral (ARV) therapy?
6. How do we stop her vaginal bleeding and epistaxis?

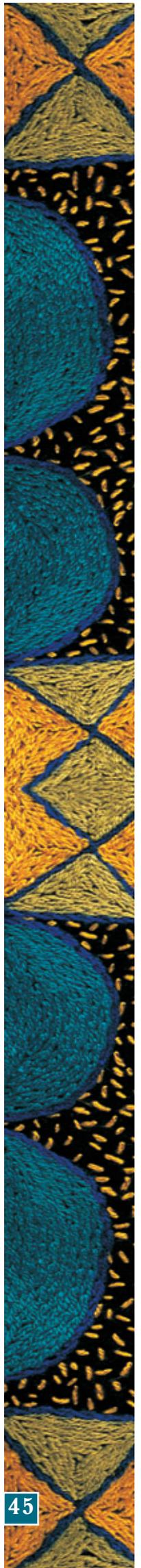
The participants were: Ifedayo Adefita, Helena Rabe, Richard Cooke, Joseph Matare, Dr Awe, Cosmas Ekeziem, Lawrence Peiperl, Mark Cotton, Brian Monaisa, Dennis Nansera, Fredrick Sinyinza and Shaffiq Essajee.

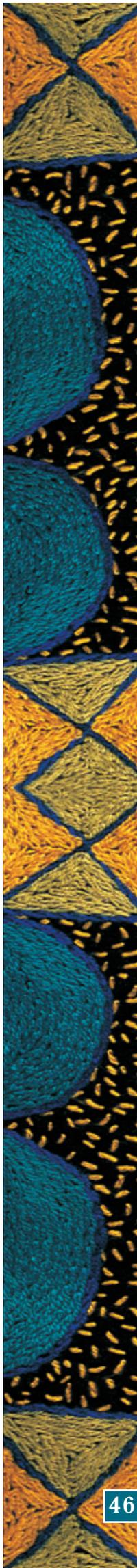
QUESTION 1: WHAT IS CAUSING THE PERSISTENTLY LOW PLATELETS?

Most participants agreed that this is probably immune thrombocytopenic purpura (ITP) secondary to HIV. Several participants pointed out that without more information, such as whether there have been acute episodes with generalised petechiae and purpura, and without a complete drug history, the cause of the ITP cannot be confidently diagnosed. Among other possible explanations for the low platelet count were systemic lupus erythematosus (SLE) and Evan's syndrome, although her age suggests that neither of these are likely explanations. All participants approached the rest of the questions from the perspective that they were treating ITP secondary to HIV.

QUESTION 2: WHY HAS THERE BEEN NO RESPONSE OF HER THROMBOCYTOPENIA TO PREDNISOLONE?

Many participants pointed out that HIV-related thrombocytopenia rarely responds to steroid therapy. Several





also felt that perhaps the patient had been put on too low a dose (dosage information was not provided), and that a course of short-term, high-dose steroids might be effective. This concerned others, as her CD4 percentage was 32%. The immunosuppression caused by steroid medications could have exacerbated her susceptibility to opportunistic infections. Some discussants suggested trying one single high dose. Others felt that administering high-dose pulsed steroid therapy would be the most appropriate treatment, and still others said that constant, high-dose steroid therapy is useful in treating thrombocytopenia. One participant cited cases in which steroids work in 40 – 80% of people with ITP secondary to HIV, but that the response can take time. *About half of the participants felt that trying another, higher dose prednisolone regimen was a good first step in addressing the thrombocytopenia.* There was no agreement on whether this therapy should be a short- or long-term course.

QUESTION 3: WHAT OTHER TREATMENT OPTIONS ARE AVAILABLE FOR HER THROMBOCYTOPENIA?

Intravenous immune globulin (IVIG) is a common treatment for idiopathic thrombocytopenia. In resource-poor settings, anti-Rh (anti-D) immunoglobulin may be an appropriate substitute. While IVIG may be expensive in the short course, if it delays the need to start ARV therapy, its use can be cost-effective. *There is a strong body suggesting that ARV regimens containing zidovudine (ZDV) or ZDV monotherapy could be effective in reversing immune-related thrombocytopenia.* This issue is complicated, of course, by the patient's eligibility for ARV therapy. A few providers suggested platelet infusion. However, the majority agree that this would probably not be successful in raising her platelet count for any significant period of time.

Many participants felt that, after finding steroid therapy unsuccessful, it would be valuable to try IVIG therapy. Others thought it unnecessary, and felt that the patient should be put on ARV therapy immediately. *All agreed that a splenectomy would be a last-resort option with many associated risks.*

QUESTION 4: AT WHAT STAGE IS HER HIV INFECTION?

At 13 the patient is a borderline adult, yet she falls under paediatric guidelines. *Strictly speaking, she is a WHO paediatric stage 3 HIV patient (unexplained thrombocytopenia $< 50 \times 10^9/l$ for more than 1 month).* She is CDC category B. Her CD4 cell count is relatively high and her viral load relatively low. Were it not for the thrombocytopenia she would fall into stage 1.

QUESTION 5: IS SHE ELIGIBLE FOR ARV THERAPY?

Whether the patient is a candidate for ARV treatment (ART) depends on which stage she is in, as well as which guidelines are being used to evaluate her eligibility. As noted, immunologically she is doing quite well and, given these indicators, does not qualify for ART. Under WHO guidelines she is in paediatric stage 3, which normally would make her eligible. *However, new WHO guidelines state that for stage 3*

patients ART should be initiated guided by CD4 cell count/percentage if the patient has thrombocytopenia and if CD4 cell counts are available. This patient's CD4 count does not indicate that ART is needed according to the WHO guidelines. This confusion is compounded by the fact that ART is probably what she needs to resolve her thrombocytopenia. South African Department of Health Guidelines and the South African HIV Clinicians Society Paediatric ART Guidelines do include thrombocytopenia as an indication for starting ART.

QUESTION 6: HOW DO WE STOP HER VAGINAL BLEEDING AND EPISTAXIS?

All participants agreed that the girl should be treated with tranexamic acid to stop her bleeding. Some suggest iron supplements, as she is clearly anaemic.

EXPERT OPINIONS

After the paediatricians had discussed the case and contributed their suggestions for treatment, the discussion was given to a panel of experts. Their background and opinions are as follows:

Expert Panel:

- Elaine Abrams, MD, Director of the MTCT-Plus Initiative and Professor of Pediatrics and Epidemiology at the Columbia University College of Physicians and Surgeons and the Mailman School of Public Health, Harlem Hospital Center, New York.
- Stephane Blanche, MD, Hospital Necker-Enfants Malades, Paris, French Pediatric HIV Study Group.
- Mark Kline, MD, Professor of Pediatrics, Chief of Retrovirology Clinic at Texas Children's Hospital, Director, Baylor International Pediatric AIDS Initiative Assistant.
- Andy Pavia, MD, Chief of Pediatric Infectious Diseases and Professor of Pediatrics and Medicine at the University of Utah.
- Ann Melvin, MD, Associate Professor, Department of Pediatrics, Division of Infectious Diseases, Children's Hospital and Regional Medical Center, University of Washington.

The experts all agreed that starting the girl on ART is the best approach to resolving the thrombocytopenia. Mark Kline suggested, based on anecdotal evidence, that ZDV-containing regimens have a more pronounced effect in reversing HIV-induced thrombocytopenia than regimens that contain stavudine. Drs Abrams, Blanche, Pavia and Melvin all felt that results should be seen within 4 – 8 weeks of initiating ART. Dr Kline believed that results could take as long as 20 weeks to be seen. *If the girl does not respond to ART within a few months, all physicians believed that she should be evaluated for lymphoma, lupus, and cytomegalovirus infection.* If ART does not resolve the thrombocytopenia, Dr Blanche believed that repeated, short prednisolone or IVIG treatments could be helpful, but that ART would probably be the best treatment.

CONCLUSION: WOMEN, CHILDREN, AND HIV ANALYSIS

Thrombocytopenia may be a presenting complaint of HIV infection. It may result from the direct effects of HIV, opportunistic infections of the marrow, autoimmune destruction, sequestration in the spleen or ARV medication; rarely, it may be an artefact caused by platelet clumping in EDTA anticoagulated samples.¹ HIV immune complexes containing antibody to envelope glycoproteins may nonspecifically deposit on platelet membranes causing their removal by the reticuloendothelial system. Direct infection of megakaryocytes may be an additional cause of thrombocytopenia. An immunological/virological mechanism for HIV-associated thrombocytopenia is suggested by the observation that patients with ITP often respond to zidovudine with doses insufficient to control HIV progression and that patients who are treated with ART rarely develop ITP. The mechanism may be reduced HIV immune complex adherence to platelets. Others causes of ITP such as SLE are easily ruled out using antinuclear antibody testing. Malignancies should be considered when ITP does not respond to standard therapy.

Before availability of ART, thrombocytopenia was a common presentation of HIV infection in children and adults. In a study of 1 118 children born to HIV-infected women in the USA, 11% had thrombocytopenia as defined by platelet counts $< 150 \times 10^9/l$.² Additional studies from the USA, Europe and resource-poor countries indicate that thrombocytopenia may occur in a cumulative incidence of 43% to 27% of adults and children respectively.^{3,4} Thrombocytopenia is listed as an AIDS-defining illness in both CDC and WHO classifications but the data on the association of thrombocytopenia and progression to AIDS are conflicting, with some studies indicating that it is associated with rapid progression and others that there is little association with progression to AIDS.^{5,6} Studies of ITP in both HIV-infected and uninfected children are, however, in agreement that the mortality rate can be high as a result of spontaneous and unexpected bleeding.⁷⁻⁹ The presence of uncontrolled ITP, especially when the platelet count is $< 30 \times 10^9/l$ should therefore be considered an urgent clinical condition and appropriate treatment should be provided.

Treatment of thrombocytopenia includes corticosteroids, IVIG, Rho (D) immunoglobulin, cytotoxic agents, plasmapheresis, interferon (IFN)-alpha and splenectomy, and for HIV infected children, ART.⁴ Many of these choices, such as splenectomy and cytotoxic agents, are contraindicated or considered a last resort in HIV-infected children. Studies in HIV-infected children with ITP show that they often respond to treatment with IVIG, Rho immunoglobulin or IFN-alpha; however, responses are often not maintained, with a failure rate over time that may be as high as 90%.^{8,9}

Given the high mortality rate of ITP as a result of spontaneous unexpected bleeding, the potential detrimental side-effects and high cost of alternative treatments, and the observations that most individuals with HIV-associated ITP respond to ART with prolonged remissions, ART should be considered the treatment of choice in this patient regardless of her CD4 count or other associated laboratory or clinical findings.

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