Case Report

Autoimmune Hemolytic Anemia as Paraneoplastic Phenomenon in Hodgkins Lymphoma in children – a rare occurrence

Jagadhesswari Sengottaiyan[1], Dhaarani Jayaraman[2], Sujith Kumar[3], Sri Gayathri Shanmugam[4*], Julius Xavier Scott[5]

[1]*Postgraduate, Department of Pathology, Sri Ramachandra Medical College and Research Institute, Chennai, India.*
[2]*Department of Pediatric Hematology and Oncology, Sri Ramachandra Medical College and Research Institute, Chennai, India.*
[3]*Department of Pediatrics, Sri Ramachandra Medical College and Research Institute, Chennai, India.*
[4]*Department of Laboratory Medicine, Sri Ramachandra Medical College and Research Institute, Chennai, India.*
[5]*Department of Pediatric Hematology and Oncology, Sri Ramachandra Medical College and Research Institute, Chennai, India.*

Article Info

Author of correspondence:
Dr. Sri Gayathri Shanmugam, Associate Professor,
E-mail: srigayathri@sriramachandra.edu.in;
Tel.: +91-9841129271;
Address:
Department of Laboratory Medicine, Sri Ramachandra Institute of Higher Education and Research (SRIHER), No.1, Ramachandra Nagar, Porur, Chennai - 600116.

Keywords

Autoimmune Hemolytic Anemia(AIHA), Hodgkin Lymphoma , paraneoplastic phenomenon, autoantibodies.

INTRODUCTION

Autoimmune disorders have been described in children with Hodgkin Lymphoma including autoimmune haemolytic anaemia [AIHA], autoimmune neutropenia, and immune thrombocytopenic purpura [ITP]. The mechanism of AIHA's association with Hodgkin's Lymphoma is not very clear. It has been thought to be due to the autoantibodies produced by tumour cells or as a Para neoplastic phenomenon, or immunity to tumour cells may cross-react with antigens on the red cells [1]. The association of AIHA with lymph proliferative disorders has been well recognized however its association with Hodgkin Lymphoma is rarely reported particularly in children [2]. Eisner et al first reported the association of Hodgkin's disease with immune haemolytic anaemia in 1967 [3].

In this case report, we describe the presentation of AIHA, subsequently diagnosed with Hodgkin Lymphoma.

CLINICAL-DIAGNOSTIC CASE

An 11-year-old boy presented with complaints of right-sided neck swelling and intermittent fever for 2 weeks. The child was well 2 weeks ago with no other significant complaints. On examination, multiple enlarged matted cervical lymph nodes were noted on the right side of the neck measuring approximately 5x3cm, which was non-tender and firm in consistency. A few isolated lymph nodes were also palpable on the left cervical region. No hepatosplenomegaly was noted. The rest of the examination was unremarkable. Baseline investigations done showed haemoglobin 6.3g/dl, mean corpuscular volume 95.4fl, mean corpuscular haemoglobin 22.2pg, mean corpuscular haemoglobin concentration 30.2g/dl, total white blood cell count 4.65 x 10^9/L with neutrophils-55.1% and lymphocytes-32.7%, platelet count 386 x 10^9/L and erythrocyte sedimentation rate-65mm/hour [shown in Table 1]. The basic biochemical analysis was also within the normal limits. Viral serologies were negative for HIV, HBsAg, and HCV. Computed tomography [CT] scan neck showed right cervical and axillary lymphadenopathy. PET CT revealed multiple FDG avid enlarged lymph nodes in the right upper, middle & lower deep cervical, right posterior

triangle, right axillary, right infraclavicular, and splenic hilum region with the largest node measuring 3.1x3cm and smallest measuring 1.5x1.5cm, suggestive of Lymphoma-LUGANO stage III. We planned for an excision biopsy of the right cervical lymph node along with bone marrow aspiration and biopsy to confirm the diagnosis. When cross matching was done before excision biopsy, there was a difficulty recognized in identifying the compatible packed red cell units. Further autoimmune workup was started, direct coombs test [DCT] was positive, peripheral smear showed microcytic hypochromic anaemia, reticulocyte count was 2.3%, there was mild indirect hyperbilirubinemia and serology for antinuclear antibodies was negative. The coagulation profile was within normal limits. The least incompatible blood unit was transfused immediately after the diagnostic procedure was completed under the cover of intravenous methylprednisolone. Histopathological examination of the right cervical lymph node excision specimen depicted effaced architecture of the node consisting of scattered large, atypical cells with nucleate and mononuclear forms resembling Reed Sternberg [RS] cells in a background of paucity of inflammatory cells composed of lymphocytes, plasma cells and occasional neutrophils with diffuse fibrosis [Figure 1, 2]. These typical morphological features are suggestive of classic Hodgkin Lymphoma – Lymphocyte depleted type, further immunohistochemical [IHC] markers were done to confirm the same and to check for the EBV association. By IHC, the large atypical cells were positive for CD15, CD30, EBV-LMP, weak positive for PAX-5, negative for CD45 and the background T & B lymphocytes were positive for CD3 and CD20 respectively which confirmed the above findings. Bone marrow examination was also normal. With this clinical presentation, laboratory investigations and histopathological findings were consistent with that of classic Hodgkin Lymphoma presenting with autoimmune haemolytic anaemia as an association. The patient was started on chemotherapy OEPA [vincristine, etoposide, doxorubicin, and Prednisolone] as per Euronet protocol and he showed a dramatic clinical response with a significant reduction in the size of nodes and improvement in haemoglobin after 1st cycle of chemotherapy.

DISCUSSION

Association of Lymphomas with syndromes of immune dysregulation and B-cell immunodeficiency are well known. Autoimmune manifestations and paraneoplastic features have been described with Hodgkin's Lymphoma commonly, however, are rare in children [2]. Levine et al in their retrospective study of adults with Hodgkin's Lymphoma in the records of 71 cases found Direct Coombs test was positive in seven who had advanced disease of which four had mixed cellularity and three had nodular sclerosis. Coombs test was positive at the time of initial diagnosis in three and at the time of relapse in others [4]. No specific studies in children for incidence are found except for anecdotal case reports.AIHA in Hodgkin's Lymphoma may present concurrently at the time of initial diagnosis of Hodgkin's Lymphoma, during the disease, or rarely can be preceding the diagnosis of Hodgkin's Lymphoma/ relapse as well [5, 6].

Chu observed AIHA in three children with Hodgkin's disease over 7 years [7]. Sierra found that advanced Hodgkin disease particularly nodular sclerosis or mixed cellularity types have a stronger association with AIHA [8]. Apart from autoimmune haemolytic anaemia various immunologic abnormalities, including autoimmune hepatitis, Hashimoto's thyroiditis, and ITP have been reported mostly in adults [9]. We have published a rare association of Hodgkin's Lymphoma with nephrotic syndrome presenting concurrently at the time of diagnosis in an adolescent boy [10]. In rare situations, Hodgkin's Lymphoma associated with AIHA may be Direct antiglobulin test negative possibly due to very low levels of IgG or low affinity bound IgG antibodies which might have been washed away during pre-test processing, or non-IgG antibodies like IgA or IgM [10]. The symptoms of AIHA a not directly related to Hodgkin lymphoma and it gets resolved after the treatment of Hodgkin lymphoma. Hence AIHA is considered a Para neoplastic phenomenon in Hodgkin's lymphoma. Treatment of Hodgkin's Lymphoma is the mainstay of therapy for associated AIHA. Anaemia or other autoimmune cytopenias usually responds to the management of the underlying malignancy and in our case, steroids being the backbone of management of Hodgkin's lymphoma, was useful for both.

TAKE HOME MESSAGES/LEARNING POINTS

Though rare, awareness of the association between Hodgkin lymphoma and autoimmune haemolytic anaemia or other autoimmune manifestations in paediatric practice is crucial since recognition of this association is the key to appropriately evaluating before starting steroids. Steroids mask the diagnosis and may lead to inadvertent delays and significantly affect the outcomes. Clinical examination for lymphadenopathy and organomegaly and appropriate investigations like chest X-ray, abdominal sonogram, or bone marrow studies should be considered before starting a patient on steroids.

Disclosures

This complies with the ethical principles for medical research involving human subjects, by the Declaration of Helsinki.

Conflicts of Interests

None

Author Contribution

JS and SK collected the data and prepared the initial draft. DJ and SG contributed to the review, editing, and final proofing of the draft. All the authors have checked the final manuscript and accepted it.

Table 1: Salient laboratory features at diagnosis

Hemogram	**At diagnosis**	**Reference intervals**
Hemoglobulin	6.3 g/dl	11.5-15.5 g/dl
Mean corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH) Mean Corpuscular HB Concentration (MCHC)	95.4 fl 22.2 pg 30.2 g/dl	77-95 fL 25-33 pg 31-37 g/dl
WBC and differentials	4.65 x 109/L (P : 55.1 % ; L : 32.7 %)	4.5-13.5 x 10^9/L (P : 50-60 % ; L : 24-54 %)
PLT	386 x 10^9/L	150-450 x 109/L
Peripheral smear	Macrocytic anemia; no blasts	Normal study
Reticulocyte count	3.6%	0.5% - 2.5%
Direct Coomb's test	POSITIVE	Negative
CRP ESR	0.8 U/L 65mm/hr	<0.8 U/L 4-10mm/hr
LDH Uric acid	670 U/L 5.6mg/dl	208-378 U/L 3.5- 7.2 mg/dl
Liver function tests	SGPT – 55U/L Albumin – 3.1g/dl Globulin – 3 g/dl Bilirubin - 2.4/ 1.6 mg/dl (total/indirect)	SGPT – 13 - 45 U/L Albumin – 3.5 -5.2 g/dl Globulin – 2 - 3.5 g/dl Bilirubin - 0.3 -1.2mg/dl (total/indirect)
Creatinine	0.4 mg/dl	0.3-0.77 mg/dl

References

1. Burley NB, Dy PS, Hande S, Kalantri S, Mohindroo C, Miller K. Autoimmune Hemolytic Anemia as Presenting Symptom of Hodgkin Lymphoma. Case Rep Hematol. 2021:5580823.
2. Ertem M, Uysal Z, Yavuz G, Gözdaşoğlu S. Immune thrombocytopenia and hemolytic anemia as a presenting manifestation of Hodgkin disease. Pediatr Hematol Oncol. 2000;17(2):181-5.
3. Eisner E, Ley AB, Mayer K. Coombs'-positive hemolytic anemia in Hodgkin's disease. Ann Intern Med. 1967;66(2):258-73.
4. Levine AM, Thornton P, Forman SJ, Van Hale P, Holdorf D, Rouault CL, Powars D, Feinstein DI, Lukes RJ. Positive Coombs test in Hodgkin's disease: significance and implications. Blood. 1980;55(4):607-11.
5. Lechner K., Chen Y.A. Paraneoplastic autoimmune cytopenias in Hodgkin Lymphoma. Leuk Lymphoma. 2010;51:469–474.
6. Gomes MM, Oliva T, Pinto A. Autoimmune Hemolytic Anemia and Hodgkin's Disease: An Unusual Pediatric Association. Case Rep Pediatr. 2016;2016:4598587.
7. Chu JY. Autoimmune hemolytic anemia in childhood Hodgkin's disease. Am J Pediatr Hematol Oncol. 1982;4(2):125-8.
8. Sierra RD. Coombs-positive hemolytic anemia in Hodgkin's disease: case presentation and review of the literature. Mil Med. 1991;156(12):691-2.
9. Saitoh T, Matsushima T, Saito Y, Yamane A, Yokohoma A, Irisawa H et al. Hodgkin Lymphoma presenting with various immunologic abnormalities, including autoimmune hepatitis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, and immune thrombocytopenia. Clin Lymphoma Myeloma. 2008;8(1):62-4.
10. Padmanaban PD, Jayaraman D, Shanmugam SG, Geminiganesan S 2022, Nephrotic syndrome and Hodgkins Lymphoma - an unusual association, eJIFCC. 33:3, 262-267.