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Where is the thin line between diagnosis of inborn error of immunity and malignancy? A case studies

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Abstract

In this article, we aim to report a patient whom initially presented with initial symptoms suggestive of an underlying immunodeficiency, but diagnostic workups lead us towards suspecting an underlying hemato-oncologic disorder. A 17-month-old infant girl (M.A) initially presented with chronic diarrhea and failure to gain weight was referred to allergy and immunology department of Hazrat-e-Rasool hospital. Her symptoms began at around 6 months of age and she was initially 7 kg when first visited. Three months after the initial complains, alopecia and alopecia areata as well as mass-like growth in her abdomen were added to her symptoms. She then was admitted to the hospital several times to due symptoms such as dehydration, Vomiting and fever. Also 3 incidences of otitis-media treated with antibiotics and one ICU-admission due to lobar pneumonia was reported in her history. Her previous laboratory data showed microcytic anemia and thrombocytosis. She had serologic and endoscopic work-ups for celiac disease which all were negative. By the paraclinical results, almost all tests were normal, so we could rule out the primary immunodeficiencies. Due to an increase in the patient's abdominal circumference a sonographic study was performed, showing a heteroechogenous mass sized 45 x 55 millimeters at retroperitoneal area. Additional Imaging with MRI was requested and proved the previous imaging study by showing a 53 x 45 x 54 millimeters mass located at left retroperitoneum. Biopsy was performed on the mass and pathological studies proven the mass to be ganglioneuroblastoma. For additional workups patient was admitted to oncology ward however unfortunately 9 days after the biopsy was performed, patient passed.

Introduction

Immunodeficiencies are known as a group a disorders caused by disturbances in quantities and/or functional properties of innate and adaptive immune responses [1,2]. They are classified as primary and secondary if their origin is genetic material and acquired, respectively [3].

Secondary immunodeficiencies, compared to primaries, are more common and appear in an older age as a result of an external factor's effect on immune system [4].

Both primary and secondary immunodeficiencies have shown to be associated with and/or cause predisposition to complications such as recurrent infections, autoimmune disease, systemic inflammatory disease, cancers and lymphoproliferative disorders [3]. Often making them difficult to identify for physicians other than immunologists [5]. Considering the underlying immune disorder or the predominant symptom, the most frequent being antibody deficiencies, well known syndromes and phagocyte function defects, the Primary Immunodeficiencies Classification Committee of the International Union of Immunology Societies (IUIS) identifies 8 large groups of pri-

mary immunodeficiencies [3]. In contrast. Secondary immunodeficiencies are results of systemic disorders such as chronic and severe illnesses, solid tumors, chronic and acute lymphoproliferative and myeloproliferative disorders [6,7].

Most common associated hematologic manifestation with immunodeficiencies are cytopenia and immune dysregulation syndromes [5,8]. However they usually don't provoke the general susception towards their diagnosis and therefore immunodeficiencies can be underdiagnosed in these circumstances. Improving awareness amongst the clinicians whom usually visit immunodeficiency patients is of crucial importance since the early diagnosis can lead to avoidance of many early disease complications and improvement of patients prognosis as well as decreasing the economic burden of disease [9].

In this article, we aim to report a patient whom initially presented with initial symptoms suggestive of an underlying immunodeficiency, but diagnostic workups lead us towards suspecting an underlying hemato-oncologic disorder.

Case presentation

A 17-month-old infant girl (M.A) initially presented with chronic diarrhea and failure to gain weight was referred to allergy and immunology department of Hazrat-e-Rasool hospital. Her symptoms began at around 6 months of age and she was initially 7 kg when first visited. Patient had normal growth and development until her initial complaint started, fully vaccinated and without any history of hospital admissions. She was born via natural vaginal delivery, her birth weight was 3 kg and she was the 4th child of her family. Her parents were related.

Three months after the initial complains, alopecia and alopecia areata as well as mass-like growth in her abdomen were added to her symptoms. She then was admitted to the hospital several times to due symptoms such as dehydration, Vomiting and fever. Also 3 incidences of otitis-media treated with antibiotics and one ICU-admission due to lobar pneumonia was reported in her history. Her previous laboratory data showed microcytic anemia and thrombocytosis. She had serologic and endoscopic work-ups for celiac disease which all were negative.

Test results for Isohemaglutinin: Blood Group and Rh: B negative- Anti-A titer: 1/8 and Anti-B titer: negative and test results for LTT are as followed: PHA: 7.2 and BCG: 4.8.

As shown by the paraclinical results, almost all tests were normal, so we could rule out the primary immunodeficiencies. Due to an increase in the patient's abdominal circumference a sonographic study was performed, showing a heteroechogenous mass sized 45 x 55 millimeters at retroperitoneal area. Additional Imaging with MRI was requested and proved the previous imaging study by showing a 53 x 45 x 54 millimeters mass located at left retroperitoneum. Biopsy was performed on the mass and pathological studies proven the mass to be ganglioneuroblastoma. For additional workups patient was admitted to oncology ward however unfortunately 9 days after the biopsy was performed, patient passed.

Test results for Isohemaglutinin: Blood Group and Rh: B negative- Anti-A titer: 1/8 and Anti-B titer: negative and test results for LTT are as followed: PHA: 7.2 and BCG: 4.8.

Table 1: Initial workup for immunodeficiencies were as followed.

Test	Result	Unit	Reference value	Differential results
White blood cell	12.6	*1000/mm^3	4-10	Mixed: 4.9 Segment: 63.2 Lymphocyte: 31.9
Red blood cell	6.91	Mill/mm^3	4.2-5.4	
Hemoglobin	12.8	g/dl	12-16	
Hct	38.1	%	36-46	
M.C.V	55.1	fL	77-97	
M.C.H	18.5	Pgm	26-32	
M.C.H.C	33.6	%	32-36	
Platelet	759	*1000/mm^3	140-440	
RDW	24.4	%	11-16	
PDW	9.4	fL	10-17	
MPV	7.5	fL	8.5-12.5	
P-LCR	9.4	%	17-45	
ESR 1st hour	7	Mm/hr	<20	

Table 2: Initial workup for immunodeficiencies were as followed.

Test	Result	Reference value
CD3	47	55-82
CD4	23	27-57
CD8	21	14-34
CD16	9	6-31
CD56	11	
CD19	39	6-23
IgA	37 mg/dl	36-79
IgG	472 mg/dl	313-1170
IgM	192 mg/dl	46-152
IgE	3 IU/dl	
NBT	98%	>90%
DHR	160	50-200

As shown by the paraclinical results, almost all tests were normal, so we could rule out the primary immunodeficiencies. Due to an increase in the patient's abdominal circumference a sonographic study was performed, showing a heteroechogenous mass sized 45 x 55 millimeters at retroperitoneal area. Additional Imaging with MRI was requested and proved the previous imaging study by showing a 53 x 45 x 54 millimeters mass located at left retroperitoneum. Biopsy was performed on the mass and pathological studies proven the mass to be ganglioneuroblastoma. For additional workups patient was admitted to oncology ward however unfortunately 9 days after the biopsy was performed, patient passed.

Discussion

As previous studies suggest, the relationship between infections and neoplasms are bidirectional, while tumors inducing immunosuppression can cause various infections which will arise the question of whether there's an underlying immunodeficiency, chronic infections are also one of the main reasons of the neoplasms. There are many pathogenetic mechanisms involved, such as chronic inflammatory state having a potential

oncogenic feature [10]. Therefore making it difficult to determine the causality relationship in the presented case.

Prolonged illnesses, uncommon complications of infection and oncohematologic malignancies can be accompanied by underlying a causative immunodeficiencies, whether they're primary or secondary [6]. Even though the studies such as whole genome sequencing couldn't be completed due to unfortunate passing of our patient the symptoms she presented throughout her disease course strongly pointed us towards suspecting immunodeficiencies. Primary and some of the secondary paraclinical evaluations came out normal, however variable degrees of severe immunocompromise can be seen at her clinical course.

Studies also suggest that 22q11 deletion syndromes can also be associated with variable degrees of immunodeficiency, Renal cell carcinomas, neuroblastomas and malignancies of the liver and the biliary tract [11]. Further highlighting the bidirectional relationship between primary immunodeficiencies and malignancies as well as secondary immunodeficiencies and neoplasms.

Conclusion

A clinical suspicion to immunodeficiencies due to their wide range of clinical presentations are difficult, but underlying neoplasms should always attract the attention of physician to them. If the primary cause of immunodeficiency is unknown, chronic illnesses and malignancies in children are best to be ruled out.

Declarations

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