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UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE PRESENTING AS AUTOIMMUNE HEMOLYTIC ANEMIA.

General Medicine

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ABSTRACT

Autoimmune hemolytic anemia occurs when antibodies directed against the person's own red blood cells cause them to burst, leading to anemia. We are presenting a case of 35 year old female who had presented with 1 month history of dyspnoea on exertion and generalized weakness without any significant past history and was eventually diagnosed as having Autoimmune Hemolytic anemia and upon further investigations was diagnosed with undifferentiated connective tissue disease(UCTD) as the cause of AIHA.

KEYWORDS

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) can be due to warm or cold autoantibody types and rarely, mixed types. AIHA presents as a triad of Anemia, jaundice and splenomegaly. Warm antibody AIHA may be seen in isolation (and it is then called *idiopathic*) or as part of a systemic auto-immune disorder such as systemic lupus erythematosus or other CTDs (sometimes AIHA may be the first manifestation that leads to a diagnosis of systemic CTD).

Some patients meet criteria for more than one defined connective tissue disease (CTD) Like SLE, while others have several symptoms characteristic of autoimmune diseases yet cannot be definitively classified. UCTD has been defined as having signs & symptoms which are consistent with a CTD but that does not fulfil the criteria for any of the defined CTDs(i.e. RA,SLE, SSc, PM/DM,MCTD,SS).

CASE REPORT

A 35 year old female, Presented to the emergency room with c/o generalized weakness and dyspnoea on exertion since 1 month. Patient did not have any complaint of palpitation, fever, jaundice, dark stools, cough, chest pain, joint pain, rashes or any history of surgery. Patient had a history of jaundice 6 years back. On examination, she had severe Pallor with tachycardia and Cardiovascular system evaluation revealed normal heart sounds with Ejection Systolic Murmur in left parasternal border. Alimentary system examination revealed moderate splenomegaly and hepatomegaly which was palpable upto 7 cm below costal margin. There was mild icterus but no cyanosis or clubbing.

On admission, her hemoglobin was 2.9 g/dL, MCV was 126 with a total leukocyte count 6,560/cumm and platelet count of 2,64,000/cumm & Peripheral blood smear showing features of Macrocytosis, Polychromasia, Anisocytois and Autoagglutination with Clumped RBCs. Serum creatinine was 0.7 mg/dL. Serum uric acid and serum electrolytes were within normal limits. Her serum bilirubin was 5.69 mg/dL (direct bilirubin - 1.09, indirect bilirubin – 4.6) with aspartate aminotransferase (AST) 145.4 IU, alanine aminotransferase (ALT)-35.4 IU, and alkaline phosphatase - 71.7 IU. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) values were also within normal range. Serum iron, vitamin B12 and TSH were normal with High ferritin(527.6). Peripheral smear for malaria and serology for dengue, viral hepatitis, chikungunya, and HIV were negative. Rheumatoid factor and anti-CCP were negative. Urine and blood culture were sterile. Chest X-ray revealed clear lung fields. Ultrasonography showed moderate hepatosplenomegaly. Her electrocardiogram (ECG) and echocardiogram (ECHO) were normal. She was advised packed red blood cell transfusion, but the blood bank informed us about difficulty in cross matching due to presence of Autoagglutination of RBCs in patient's blood. This led us to suspect AIHA. Further investigations revealed a reticulocyte count of 9% and Strong positive (+4) Direct Coombs Test. Serum bilirubin raised to 7.55 (direct - 1.55, indirect – 6.0), but liver enzyme levels remained within normal limits. Serum lactate dehydrogenase (LDH) was 1111. Urine examination did not show RBCs or hemoglobin. Antinuclear antibody by IF was +3 intensity, Speckled pattern. Serum complement levels were low. ANA Blot revealed Specific Bands for Anti U1RNP 68kD, Sm/RNP,F-Actin antibodies and SSA/RO 52 K(weak) Antibodies. One unit of least incompatible packed red cells were transfused with premedication. Since the reports were in favor of a hemolytic process, we started inj. methylprednisolone 1000 mg as intravenous pulse(Methyl Prednisolone Pulse Therapy). Follow-up investigations showed significant improvement in haemoglobin(Hb rose to 9.5 g/dL with 1 pint of PCV and MPPS). After 3 days of pulse, she was switched over to tapering doses of oral prednisolone.

Since the Patient was not fitting into Criteria for any Definitive Connective Tissue Disorder , the Diagnosis of Undifferentiated Connective Tissue Disorder was made based on Symptoms and High Titres of Multiple antibodies. Patient was Started on Hydroxychloroquine for that and Tapering Doses of Oral Steroids. She is doing well and is on regular follow-up.

DISCUSSION :

Autoimmune haemolytic anemia is often abrupt in onset. AIHA has been known to occur in 5%–10% of patients of Connective tissue diseases. AIHA is a rare disease with an incidence of 1–3 per 1,00,000 people per year. AIHA consist of warm, cold, or mixed reactive antibody types that are directed against antigens on the red blood cell surface. Cold AIHA is distinguished from warm AIHA by a preponderance of immunoglobulin M autoantibodies known as cold agglutinins (CAs) that react strongly between 0°C and 4°C. Cold AIHA can be primary or idiopathic and secondary to infection, malignancy or autoimmune conditions. Pathophysiology is based on molecular mimicry of foreign antigens. CAs activates classical complement pathway, leading to C3b deposition on the surface of red blood cells, which are phagocytosed in the liver.The direct Coomb's test is practically diagnostic of AIHA. There are different modalities of AIHA treatment, which includes corticosteroids, rituximab, IV immunoglobulin, or splenectomy. Patients can be classified as UCTD if they fulfil the criteria as follows: (1) signs and symptoms suggestive of a connective tissue disease (CTD), but not fulfilling criteria for a defined CTD, (2) positive antinuclear antibodies on two separate measurements controls and (3) a disease duration of at least 3 years. If

the disease duration is less than 3 years, it may be defined as Early UCTD. These criteria strongly rely on the absence of other SADs (Systemic Autoimmune Diseases), that is the inability to fulfil other classification criteria for major CTDs. Not surprisingly, literature data show that up to 30% of UCTD may evolve into a definite 'major' SAD within few years from the diagnosis (all reviewed in). Our patient had symptom duration of 1 month without any Prior significant History and on Further investigating , She had multiple Antibodies Positivity on ANA blot which led us to the diagnosis of Early Undifferentiated Connective tissue Disease in the absence of any SAD. Patient may progress to any defined SADs in future.

Image	No	Name	A(U/ml)	B(U/ml)	C(U/ml)	Mean	Result	CO value	Std dev
									
		First RC	78 AU	78 AU	76 AU	77 AU			0.83
	1	Negative	3	3	3	3		6.00	0.16
	2	dsDNA	3	1	1	2	-	6.00	0.75
	3	Histones	12	6	5	8	(-)	6.00	3.19
	4	Sm	7	3	1	5	(-)	6.00	1.78
	5	RNP 68kDA/C	71	64	60	67	+	6.00	2.49
	6	Sm/RNP	90	89	93	91	+	6.00	1.73
	7	SSA/Ro 60kD	6	3	4	4	-	6.00	1.22
	8	SSA/Ro 52kD	8	7	7	7	+	6.00	0.23
	9	SSB	5	2	2	3	-	6.00	1.45
	10	Scl 70	5	3	3	4		6.00	0.92
	11	Ku	7	4	2	5	(-)	6.00	1.68
	12	PM Scl 100	4	2	2	3		6.00	0.66
	13	Mi-2	5	3	3	4	-	6.00	1.30
	14	Jo 1	5	3	3	3		6.00	0.98
	15	PL-7	6	3	3	4	-	6.00	1.48
	16	PL-12	5	3	3	4	-	6.00	0.93
	17	SRP-54	3	2	2	2	-	6.00	0.30
	18	Ribosomes P0	2	1	1	1	-	6.00	0.49
	19	CENT-A/B	4	2	2	3	-	6.00	0.85
	20	PCNA	4	2	2	2		6.00	0.93
	21	sp100	1	1	1	1	-	6.00	0.09
	22	gp210	2	1	2	2		6.00	0.48
	23	M2 recombinant	2	1	2	1	-	6.00	0.21
	24	M2 native	4	3	6	5	-	6.00	1.28
	25	F-actin	75	56	75	69	+	6.00	8.95
		Cal. 0 U/ml	0 AU	0 AU	0 AU	0 AU			0.00
		Cal. 6 U/ml	21 AU	16 AU	20 AU	19 AU			2.02
		Cal. 12 U/ml	28 AU	22 AU	28 AU	26 AU			2.93

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CONCLUSION:

Since AIHA associated with any Connective tissue disorder is better managed with control of CTD, Every patient Diagnosed of having AIHA warrants detailed investigation. In view of Multiple Antibody Postivity and Short duration of History, Patient in future may Progress to any one of the Defined CTDs.

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