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Chronic Immune Thrombocytopenic Purpura in a Young Female with Rheumatoid Arthritis (Unusual Course)

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Abstract

We present a case of a 29-year-old female from Sudan, who was diagnosed with rheumatoid arthritis (RA) in 2005 and with immune thrombocytopenic purpura (ITP) in 2009. The ITP immediately followed using, for four weeks, a combination of medications that included rifampicin. The platelets count continued to be low thereafter. During the year following her diagnosis with ITP, she reported gradual improvement in her joints symptoms, which continued during her pregnancy in 2011. Following puerperium, her chronic ITP resolved completely; however, her joint disease flared up few months later. To our knowledge, there are no reported cases of chronic ITP, which were drug induced at first in a patient of RA except with gold therapy. Similarly, there are no reports on cases that recovered from chronic ITP after delivery. Finally, this case highlights the impact different coexisting autoimmune diseases may have on each other regarding course and prognosis.

Keywords

ITP, Immune Thrombocytopenic Purpura, Drug-Induced Thrombocytopenia, DITP, Pregnancy, Rheumatoid Arthritis

1. Introduction

The occurrence of chronic Immune Thrombocytopenic Purpura (ITP) in association with Rheumatoid Arthritis (RA) is a rare entity, but has been reported in literature [1]-[9]. Similarly, drug induced thrombocytopenia in patients with RA has also been reported with various medications including disease modifying antirheumatic drugs (DMARDs) and Biologics [10]-[23]. The significance of re-

porting this case is to cast light over an unusual persistence of thrombocytopenia in a patient with RA, which appears most likely drug induced. It also raises an intriguing question about the prognosis of autoimmune diseases in general: the appearance and disappearance of ITP was preceded by using a regimen that included rifampicin and childbirth respectively, which may suggest causation. Furthermore, this case illustrates an unusual impact of a secondary autoimmune condition (ITP) on a pre-existing primary autoimmune condition (RA) with regards to the severity and activity of the latter. The mechanisms that may have underpinned this is unclear; however, it is possible that it involved complex immunological mechanisms.

2. Case Presentation

In March 2005, a young female doctor was diagnosed with RA at the age of 23,based on having more than two months history of multiple joints pain, swelling, and morning stiffness lasting more than an hour. The symptoms mainly involved the small joints of both hands and wrists. Other features were strongly positive rheumatoid factor, high antinuclear antibody titre at 1/160 and family history of autoimmune diseases. Anti cardiolipin and lupus anticoagulant were negative, other serology were not available. Routine blood tests and hands x ray were normal. In subsequent visits, she was prescribed sulfasalazine 500 mg once daily for a week then increased gradually to 1 gram twice daily over a month. At some point, she was prescribed methotrexate, but she deferred using it.

In 2009, she self-prescribed a regimen in an attempt to treat her arthritis. This treatment was based on a theory originally conceived and presented by Dr Roger Wyburn-Mason who suggested that all rheumatic diseases are caused by amoeba and thus can be neutralized by using antibiotics. The regimen used by the patient included rifampicin 600 mg once a day for a month, metronidazole 2 g for two days in a week for a month and allopurinol 300 mg daily for a week. Two weeks after the regimen had ended; she started experiencing easy bruising and petechial rashes appearing on both thighs and arms with minor trauma. These got worse during the next two weeks; they occurred spontaneously and became much larger and associated with gum bleeding without provocation and menorrhagia. She was off medication during that period except for paracetamol, when needed. A complete blood count turned out to be normal apart from a very low platelets count of $4 \times 10^3/\mu L$. She was transfused two pints of platelets at a local hospital in Sudan, as intravenous immunoglobulin (IVIG) was very expensive and difficult to obtain. A bone marrow examination was suggested after repeating her labs (Table 1), however, the patient refused and opted to start corticosteroids at her own. Her platelet count increased gradually with prednisolone 40 mg once daily, and after two weeks, it reached $63 \times 10^3/\mu L$, only to drop to below $20 \times 10^3/\mu L$ after tapering the steroids.

During the year 2010, she was constantly anaemic (haemoglobin levels between 8.5 to 9.8 g/dl) due to menorrhagia and occasional mild nose and gum

Table 1. Laboratory values at diagnosis of ITP.

Laboratory test	Value	Reference Range
	Haematology	
Haemoglobin (g/dl)	12.6	11.0 - 16.0
Haematocrit (%)	40.8	35.0 - 48.0
RBC (Million/μL)	4.49	4.5 - 5.5
MCV (fl)	90.9	80.0 - 92.0
MCH (pg)	28.1	27.0 - 31.0
MCHC (g/dl)	30.9	31.0 - 33.0
Reticulocytes Count (%)	3	0.5 - 2.5
Platelets ($\times 10^3$/μL)	9	150 - 450
Comment	Thrombocytopenia with no aggregation	
WBC ($\times 10^3$/μL)	3.6	4.00 - 11.00
Differential:		
Neutrophils ($\times 10^3$/μL)	1.9	1.80 - 6.80
Lymphocytes ($\times 10^3$/μL)	1.5	1.20 - 4.90
Monocytes ($\times 10^3$/μL)	0.1	0.10 - 0.80
Eosinophils ($\times 10^3$/μL)	0.1	0.10 - 0.40
APTT		
APTT (Sec)	30	30 - 36
Control (Sec)	31	30 - 36
	Chemistry	
Serum Creatinine (mg/dl)	0.6	0.5 - 0.9
Blood Urea (mg/dl)	31.9	
	Immunology	
Direct Coombs Test	Negative	
	Urine Analysis	
Chemical-Macroscopic Exam		
Colour	Yellow	
Reaction	Alkaline	
Inspection	Clear	
Sugar	Negative	
Acetone	Negative	
Protein	Negative	
Bilirubin	Negative	
Urobilinogen	Normal	
Nitrate	Negative	
Microscopic Exam		
Pus cells	0 - 1	
RBC	1 - 2	
Epithelial Cells	[few]	

Continued

Crystal	Absent
Cast	Absent
Yeast cells	Absent
Mucous thread	Absent
Others	No others

BC: Red Blood Cells, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Haemoglobin, MCHC: Mean Cell Haemoglobin Concentration, WBC: White blood cells, APTT: Activated Partial Thromboplastin Time.

bleeds. Her platelet count was fluctuating between $20 \times 10^3/\mu L$ and $30 \times 10^3/\mu L$ without the use of steroids. Surprisingly, her joint pains were getting better slowly and gradually.

In 2011, she got pregnant while she was on high dose prednisolone for one month, which she took to minimize expected bleeding from a surgical tooth extraction. During her pregnancy, her platelets count continued to be less than $30 \times 10^3/\mu L$ until the last trimester when it dropped to less than $20 \times 10^3/\mu L$ (Table 2). All other ante-natal tests including trans-cranial fetal ultrasound were normal.

Six weeks before her expected date of delivery, she was started on 60 mg prednisolone daily in anticipation of labour bleeds, which rose platelets count to $260 \times 10^3/\mu L$. She gave birth to a healthy baby boy weighing 3.2 kg by normal vaginal delivery. His platelet count at delivery was normal and remained so when tested after one month. The patient continued prednisolone for another six weeks after delivery to prevent expected heavy puerperal bleeding. Surprisingly, after tapering and discontinuing the prednisolone, her platelet counts remained normal without any treatment after puerperium. It continued to be so ever since (Table 3). Conversely, as her chronic ITP ceased to be, overtime her joint pains started to reappear with a full-blown picture of RA six months after delivery.

3. Discussion

Thrombocytopenia in patients with RA has several differential diagnoses, including chronic ITP, Felty syndrome, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APLS), drug-induced thrombocytopenia (DITP), and infections. Physicians are generally able to reach the diagnosis of chronic ITP after excluding other causes of low platelets and performing sets of investigations including a bone marrow examination. Antiplatelet antibodies testing is not widely available, therefore, it is not essential for making the diagnosis. Patients with chronic ITP generally respond well to steroids and the condition is termed chronic if it continues for more than twelve months.

Certain medications are known to cause low platelets; however, the count is expected to rise shortly after discontinuing the offending drug. Although, occasionally this might not be the case and platelet count might continue to be low after drug cessation for weeks or even months. The longest period reported in

Table 2. Complete blood count at 36 weeks gestation.

Laboratory test	Value	Reference Range
Haematology		
Haemoglobin (g/dl)	11.8	12.0 - 15.0
Haematocrit (%)	37.1	36.0 - 46.0
RBC (Million/μL)	4.51	3.80 - 4.80
MCV (fl)	82.2	76.0 - 96.0
MCH (pg)	26.2	26.0 - 32.0
MCHC (g/dl)	31.8	31.5 - 34.5
RDW (%)	15.2	11.6 - 14.0
Platelets ($\times 10^3$/μL)	16.5	150 - 450
MPV (fL)	14.3	7.40 - 10.40
Comment	Marked Thrombocytopenia noted; occasional giant platelets seen	
WBC ($\times 10^3$/μL)	9.1	4.00 - 11.00
Differential:		
Neutrophils ($\times 10^3$/μL)	5.22	1.80 - 7.00
Lymphocytes ($\times 10^3$/μL)	2.97	1.00 - 4.00
Monocytes ($\times 10^3$/μL)	0.707	0.20 - 1.00
Eosinophils ($\times 10^3$/μL)	159	0.02 - 0.50
Basophils ($\times 10^3$/μL)	0.045	0.02 - 0.100

RBC: Red Blood Cells, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Haemoglobin, MCHC: Mean Cell Haemoglobin Concentration, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume, WBC: White blood cells.

Table 3. Complete blood count at eight weeks after delivery.

Laboratory test	Value	Reference Range
Haematology		
Haemoglobin (g/dl)	13.8	12.0 - 15.0
Haematocrit (%)	38.7	36.0 - 46.0
RBC (Million/μL)	4.75	3.80 - 4.80
MCV (fl)	81.5	76.0 - 96.0
MCH(pg)	29	26.0 - 32.0
MCHC (g/dl)	35.6	31.5 - 34.5
RDW (%)	12.1	11.6 - 14.0
Platelets ($\times 10^3$/μL)	317	150 - 450
MPV (fl)	8.12	7.40 - 10.40
WBC ($\times 10^3$/μL)	9.53	4.00 - 11.00
Differential		
Neutrophils ($\times 10^3$/μL)	5.47	1.80 - 7.00
Lymphocytes ($\times 10^3$/μL)	3.39	1.00 - 4.00

Continued

Monocytes ($\times 10^3/\mu L$)	0.436	0.20 - 1.00
Eosinophils ($\times 10^3/\mu L$)	0.167	0.02 - 0.50
Basophils ($\times 10^3/\mu L$)	0.063	0.02 - 0.10

RBC: Red Blood Cells, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Haemoglobin, MCHC: Mean Cell Haemoglobin Concentration, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume, WBC: White blood cells.

literature of this, to the best of our knowledge, was of a patient who continued to have low platelets for two years after sulfamethoxazole was stopped [24]. Another report demonstrated chronic thrombocytopenia lasting for 18 years after gold injection therapy in a patient with RA. However, it is worth noting that gold is known to persist in body tissues for years after injections indicating the persistence of antigens triggering thrombocytopenia [25]. There are a number of reports on rifampicin induced thrombocytopenia in patients with tuberculosis [26] [27] [28] [29], however, to our knowledge, there are no similar reports related to metronidazole. Few cases were associated with allopurinol, but these were rarely isolated thrombocytopenia [30] [31].

Well-established chronic ITP with pregnancy has been reported frequently; however, most studies focused on maternal complications, fetal outcome, and management during pregnancy and labour. To our knowledge, there are no reported cases of spontaneous improvement in platelets count after labour in patients with confirmed chronic ITP diagnosed before pregnancy, not to be mistaken with gestational or incidental thrombocytopenia, which is the commonest type of thrombocytopenia during pregnancy and could be considered as transitory physiological phenomenon during the second and third trimester [32] [33] [34].

Another key feature of this case is the gradual remission of RA symptoms after the onset of thrombocytopenia, and then the re-emergence of these symptoms few months after labour concomitantly with the return of normal platelet count. Although there was no formal assessment from a rheumatologist to confirm the alleged improvement in joint disease, the patient account confirms not having any joints pain, swelling or stiffness after a period of initial gradual improvement when she had thrombocytopenia. Reviewing the data, there are no reports of similar occurrences in patients with multiple autoimmune diseases or overlap syndromes highlighting any sort of improvement or worsening of a primary autoimmune disease after diagnosing a secondary one during its course. Nonetheless, it is well established that RA symptoms can improve during pregnancy and flare up after delivery [35] [36] [37].

Case Analysis

This case outlines a number of learning points: Firstly, it appears that in a setting of dysfunctional immunological responses and autoreactive susceptibility, drug induced thrombocytopenia may persist for more than 12 months contrary to

Table 4. Complete blood count before the regimen.

Laboratory test	Value	Reference Range
Haematology		
Haemoglobin (g/dl)	14.5	11.5 - 15.5
Haematocrit (%)	43	33.0 - 45.0
RBC(Million/µl)	5.06	3.6 - 5.01
MCV(fl)	85	80 - 99
MCH(pg)	29	27 - 32
MCHC (g/dl)	33.7	32.0 - 36.0
RDW (%)	14.6	11.5 - 15.5
Platelets ($\times 10^3/\mu L$)	298	145 - 400
MPV (fl)	9.8	7.40 - 11.30
WBC ($\times 10^3/\mu L$)	3.5	4.00 - 11.00
Differential		
Neurophils ($\times 10^3/\mu L$)	1.47	1.80 - 7.00
Lymphocytes ($\times 10^3/\mu L$)	1.82	1.00 - 3.20
Monocytes ($\times 10^3/\mu L$)	0.07	0.00 - 0.80
Eosinophils ($\times 10^3/\mu L$)	0.14	0.00 - 0.40
Basophils ($\times 10^3/\mu L$)	0.00	0.00 - 0.20

C: Red Blood Cells, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Haemoglobin, MCHC: Mean Cell Haemoglobin Concentration, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume, WBC: White blood cells.

current commonly accepted views. Despite the fact that the thrombocytopenia in our case was not confirmed to be drug induced by laboratory methods, we believe there was a strong correlation in the history between the drug administration and the fall in platelet count though symptoms were delayed for two weeks after discontinuing the regimen. In addition to the correlation, the patient provided a complete blood count result, done two weeks prior to the initiation of the offending medications, showing a normal platelet count (Table 4). One may question the possibility of overlap syndrome in this particular case, however, the administration of rifampicin just few weeks before thrombocytopenia favours DITP, which triggered chronic ITP. Secondly, the emergence of a new autoimmune condition in a patient with pre-existing one could have an impact on the former condition, which can be remission such as in this case. Thirdly, the case challenges currently held views on the prognosis of chronic ITP; which, once underlying mechanisms are established if further probed and sought, may change the management and psychological impact of the disease on those affected. The impact of pregnancy and labour on different autoimmune diseases, although poorly understood, can provide an understanding of immunological mechanisms that may underpin autoimmunity.

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Ethical Consideration

Informed consent was obtained from the patient to report the case.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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