CASE REPORT

Immune Thrombocytopenia in a worker exposed to toluene: a case report

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Abstract

Introduction: Immune thrombocytopenia (ITP) is the most common cause of isolated thrombocytopenia in healthy individuals and can be classified as either primary or secondary. Drug use is an identifiable underlying cause for ITP. Toluene is a widely used solvent that is often contaminated with small amounts of benzene, a hematotoxic agent that can cause thrombocytopenia. Herein, we report a case of ITP in a patient with long-term low-level exposure to toluene in the workplace.
Case Report: A 34-year-old white female chemistry technician presented to a teaching hospital in Rio de Janeiro, Brazil, in 2002, with a 2-year history of isolated thrombocytopenia, and low-level occupational exposure to toluene for more than a decade. She had bruises on the physical exam, and platelets count of 40.000 µL. A diagnosis of primary ITP aggravated by benzene-contaminated toluene exposure was made. The treatment included definitive removal from exposure and changes in activities, with gradual improvement in the clinical condition and platelet count, although without normalization.
Discussion: We addressed the role of benzene as a toluene contaminant and an aggravating agent of primary ITP, a multifactorial disease that arises from different mechanisms. Although several substances may cause ITP, little attention has been paid to the role of toxicants such as benzene, a well-known hematotoxic agent.
Conclusion: This case highlights the role of benzene-contaminated toluene in ITP. As benzene is a hematotoxic agent, we recommend that proper health and environmental evaluations should consider benzene exposure in workplaces where toluene is used.

Keywords: Toluene; Benzene; Occupational Exposure; Purpura Thrombocytopenic; Thrombocytopenia

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INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by platelets count of 100.000 µL, and is caused by antiplatelet autoantibodies. It is the most common cause of isolated thrombocytopenia in healthy individuals with incidence rates from 1.1 to 12.5 per 100,000 persons/year, similarly in children and adults [1,2]. Regarding its duration, ITP is termed as newly diagnosed (≤ 3 months), persistent (> 3-12 months), or chronic (≥ 12 months) [1,3]. Chronic ITP affects up to 70% of adults and has a female predominance of 2.8 for patients between 18 and 49 years [2,3]. In addition, ITP can be classified as either primary (80 %) or secondary, depending on an apparent precipitating condition such as an autoimmune disease, viral infection, or predisposing factors such as drug use [1,4].

Toluene is widely used as a solvent in many settings, like occupational (e.g. gasoline service station), domestic (e.g. stain remover), and recreational (e.g. glue sniffing). It is often contaminated with benzene even at high purity [5-7]. Although toluene is readily absorbed through ingestion, inhalation is the most common route of exposure. Most of it is biotransformed in the liver, distributed in fatty and highly perfused tissues, and excreted rapidly in urine as hippuric acid (HA-u) [5]. The nervous system is the primary target organ for toluene toxicity, and the cardiac, respiratory, and renal systems can also be compromised, but not the hematopoietic system [5,6].

Here, we present a unique case of ITP in an adult woman with a history of long-term low-level exposure to toluene at the workplace, focusing on the role of benzene-contaminated toluene in worsening platelet levels during the course of the disease. This case report highlights the need to assess benzene exposure and perform hematological tests in workers exposed to toluene.

CASE REPORT

A 34-year-old white woman, who was a chemistry technician, sought occupational medical services because of fatigue and diffuse bruising for a week. She denied fever, bleeding, or any neurological symptoms. She did not report any

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local trauma. Six months earlier, she had been diagnosed with toluene-induced hepatitis, with complete recovery after 45 days. The clinical investigation included blood tests (biochemical studies, creatinine, urea, alkaline phosphatase, liver transaminases, bilirubin, complete blood count [CBC], and coagulation screen) that showed only platelet count of 31.000 µL with normal white blood cell count (9.000 µL) and hemoglobin (13.6 g/dL). The recommendation was medical leave from work for a month, and evaluation by a hematologist who repeated the CBC, which confirmed the result. Peripheral blood film showed thrombocytopenia with no schistocytes or dysplastic changes. Common causes of thrombocytopenia like recent transfusions and vaccinations, coagulopathy, pregnancy, nutrition deficiency, hypersplenism, autoimmune diseases, hepatic or renal dysfunction, viral infections, syphilis, and toxoplasmosis were ruled out. Therefore, primary ITP was a presumptive diagnosis based on isolated thrombocytopenia, a normal peripheral blood film, and no apparent cause. High-dose oral corticosteroid was prescribed (1 mg/kg prednisone, total 80 mg) for 2 weeks, followed by gradual withdrawal. Ten days later, she felt better, the platelets count increased to 80.000 µL, and she returned to work. However, in a week, she complained of bruises, nausea, and platelets count dropped to 46.000 µL. A re-evaluation by a hematologist included a bone marrow aspiration that revealed normal numerical and cytological features of marrow cells, raising suspicion of peripheral platelets destruction. The hematologist resumed oral corticosteroids (40 mg dexamethasone for 4 days, monthly). She continued to work against medical recommendations. One month later, her clinical condition and thrombocytopenia (29.000 µL) worsened, despite the treatment. She had been on medical leave from work for 3 months. A gradual clinical improvement was observed and platelets count raised up to 50.000 µL. By the end of the third month of treatment, the corticosteroid dose was tapered off. She returned to work and over the next 18 months, the platelets count fell even further every time she returned to work (34.000 to 40.000 µL), improving after she was away (50.000 to 98.000 µL), without normalization. No other treatments were prescribed. She sought help from the Reference Center for Workers' Health, which referred her to the Toxicology Department of a teaching hospital, in 2002, with the hypothesis of toluene-induced thrombocytopenia.

At clinical evaluation, she was symptomatic and platelets was 40.000 µL. The clinical history revealed no smoking, drinking habits or drug use. She rarely consumed canned food or soda. She reported a previous cesarean section and did not remember any physicians telling her about a blood problem. No significant family history of illness was reported. Skin examination revealed ecchymosis in the abdomen and extremities. Palpable lymphadenopathy and hepatosplenomegaly were not observed.

Occupational history revealed a 40-hours weekly work schedule for 15 years in an industrial joint factory. She was responsible for controlling the production of the hydraulic cardboard and testing the toluene to be used at the facility. The American Society for Testing and Materials International (ASTM) standard test method was used to determine the distillation range of industrial aromatic hydrocarbons [8]. According to it, 2ºC is the maximum boiling point range to establish the specified purity for the industrial grade of toluene [7,9]. Noteworthy, she reported that, depending on the brand of toluene vats tested, she frequently observed a wider boiling point range, medium of 5ºC, meaning a benzene content of approximately 13% [9]. In addition, she supervised activities that included solvent mixing and spraying. The factory provided the earplugs and N95 masks. The reports of her annual occupational health surveillance revealed toluene exposure below the reference value from Regulatory Standard nº 7 of the Brazilian Ministry of Labor. The workplace air monitoring results were within the permitted thresholds stipulated by the American Conference of Governmental Industrial Hygienists (ACGIH) of 1977 adapted to Brazilian working conditions. The patient reported that biomonitoring was initiated at the beginning of weekly workdays (Table 1). No information regarding the other solvents used in the factory or the benzene content of toluene is available.

A screen for TSH was normal, and thyroid antibodies, varicella zoster serology, and Helicobacter pylori test results were negative. Additionally, anti-RNP, anti-CENP-B, anti-Sm, anti-SS-A, and anti-SS-B antibodies, was not reactive. The C3 and C4 blood test results were within normal ranges (Table 2). Therefore, based on clinical evaluation and worsening of the condition when re-exposed and improvement when on medical leave, a diagnosis of primary ITP aggravated by benzene-contaminated toluene exposure was formulated.

The case was notified as an occupational disease, group III of Schilling, to the official government, and a report requested the worker's transfer to a bureaucratic activity, which was approved by a government expert assessment [10]. The patient maintained regular medical follow-up, remaining asymptomatic and with platelets count between 68.000 and 123.000 µL (Figure 1).

Table 1. Air monitoring at the workplace and patient's biomarker of exposure

Air monitoring	Maximun Concentration Observed	Brazilian Thereshold Limit Value (TLV)*	European Union Limit Value for 8 hours
Toluene (ppm)	3	78	50
Biomarkers of exposure	Maximun Concentration Observed	Brazilian Biological Exposure Index (BEI)	European Union Biological Limit Value (BLV)
Hippuric acid (g/g Cr) – urine	1.50	2.50	-

* According to the American Conference of Governmental Industrial Hygienists of 1977 adapted to Brazilian working conditions (for 48 hours/week of work)
** According to the Brazilian Labour Ministry (Regulatory Standard nº7)

Table 2. Blood and urine exams performed during clinical investigation

	Exams	07/23/1999	09/06/1999	12/17/1999	01/10/2000	01/31/2000	04/04/2002
Hepatic tests	Blood						
	ALT (IU/L) Ref. (4-32)	710	20	30	-	-	25
	AST (IU/L) Ref. (4-36)	510	16	28	-	-	26
	ALP (IU/L) Ref. (12-43)	57	27	40	-	-	41
	GGT (IU/L) Ref. (9-36)	136	40	37	-	-	18
	Bilirrubin total (mg/dL) Ref. (<1.2)	2.6	1.0	0.9	-	-	1.0
	Bilirrubin direct (mg/dL) Ref. (<0.4)	2.1	0.8	0.2	-	-	0.2
	PT (sec) Ref. (11-13.5)	-	12.6	12	-	-	12
	INR Ref. (0.8-1.1)	-	1.1	1.14	-	-	1.0
	Protein (g/dL) Ref. (6.0-8.3)	6.9	-	7.0	-	-	7.0
	Albumin (g/dL) Ref. (3.4-5.4)	4.1	-	4.0	-	-	4.1
	Alpha-1 globulin (g/dL) Ref. (0.1-0.3)	-	-	-	-	-	0.2
	Alpha-2 globulin (g/dL) Ref. (0.6- 1.0)	-	-	-	-	-	0.6
	Beta globulin (g/dL) Ref. (0.7- 1.2)	-	-	-	-	-	1.0
	Gamma globulin (g/dL) Ref. (0.7-1.6)	-	-	-	-	-	1.1
CBC	Hemoglobin (g/dL) Ref. (12-15)	15	-	13.6	-	-	13
	Hematocrit (%) Ref. (36-44)	44	-	39	-	-	39
	WBC (per L) Ref. (4.000-10.000)	6.000		9.000	-	-	8.800
	Platelets (µl) Ref. (150.000-450.000)	190.000	-	31.000	-	80.000	40.000
	Reticulocytes (mm^3) (%) Ref. (22.000-94.000) (0.5-2.5%)	-	-	-	-	-	77.900 1.66
	Immature Reticulocyte Fraction (%) Ref. (2.1-14.9)						11.2
Coagulation screen	PTT (sec) Ref. (25-35)	-	-	30	-	-	28
	Bleeding time (min) Ref. (1-9)	-	-	4	-	-	-
	Blood clotting time (min) Ref. (4-10)	-	-	5	-	-	-
	Thrombin time (sec) Ref. (15-19)	-	-	18	-	-	17
	Fibrinogen (mg/dL) Ref. (130-330)	-	-	-	145	-	-
Renal function	Urea (mg/dL) Ref. (10-50)	-	-	20	-	-	22
	Creatinine (mg/dL) Ref. (0.50 - 1.10)	-	-	0.85	-	-	1.0
Thyroid screen	TSH (µIU/mL) Ref. (0.35-5.9)	-	-	-	-	-	4.1
	Free T4 (ng/dl) Ref. (0.7-1.8)	-	-	-	-	-	1.1
	Total T3 (ng/dl) Ref. (80-180)	-	-	-	-	-	121
	Thyroid peroxidase antibodies/thyroglobulin antibodies/Thyrotropin receptor antibodies	-	-	-	-	-	Neg
Rheumatic screen	Rheumatoid factor (IU/mL) Ref. (0-20)	-	-	-	< 20	-	< 20
	ANA (U) Ref. (<1.1)	Neg	-	-	Neg	-	Neg
	Anti-dsDNA (U/mL) Ref. (<20)	-	-	-	Neg	-	Neg
	C3 (mg/dl) Ref. (88-206)	-	-	-	-	-	90
	C4 (mg/dl) Ref. (16-48)	-	-	-	-	-	20
	Anti-Sm (U/mL) Ref. (<7)	-	-	-	-	-	Neg
	Anti-RNP (U) Ref. (<20)	-	-	-	-	-	0.7
	Anti-CENP-B (U/mL) Ref. (<10)	-	-	-	-	-	ND
	ASMA (U/mL) Ref. (<7)	Neg	-	-	-	-	-
	Anti-SS-A/Ro (U) Ref. (<20)	-	-	-	-	-	0.1
	Anti-SS-B/La (U) Ref. (<20)	-	-	-	-	-	0.1

Table 2. Continued.

	Exams	07/23/1999	09/06/1999	12/17/1999	01/10/2000	01/31/2000	04/04/2002
Infectious diseases	Anti-HIV	ND	-	-	ND	-	-
	Anti-HAV-IgM/IgG	ND	-	-	ND	-	-
	HBsAg/Anti-HBs/Anti-HBc	ND	-	-	ND	-	-
	Anti-HCV-IgM/IgG	ND	-	-	ND	-	-
	Anti-EBV-IgM/IgG	-	-	-	ND	-	-
	Anti-CMV-IgM/IgG	-	-	-	ND	-	-
	Anti-Toxoplasma-IgM/IgG	-	-	-	ND	-	-
	VDRL/FTA-ABS-IgG	-	-	-	ND	-	-
	Anti-VZV-IgM/IgG	-	-	-	-	-	ND
Others	β-Hcg (mIU/mL) Ref. (<5)	-	-	-	1.5	-	-
	B12 Vitamin (pg/mL) Ref. (210-980)	-	-	-	660	-	-
	Folic acid (µg/l) Ref. (3.10-20.50)	-	-	-	6.85	-	-
	IgA (g/L) Ref. (0.8-3.0)	-	-	-	-	-	1.0
	IgG (g/L) Ref. (6.0-16.0)	-	-	-	-	-	6.5
	IgM (g/L) Ref. (0.4-2.5)	-	-	-	-	-	0.8
	Blood group and Rh	-	-	-	-	-	A +
	Antiglobulin test (direct/indirect)	-	-	-	-	-	Neg
	Urine						
BEI	Hippuric acid (g/g creatinine) Ref. (<1.5)	0.9	-	1.3	-	-	-

Note: ALT – Alanine transaminase; AST – Aspartate transaminase; ALP – Alkaline phosphatase; GGT – Gamma- glutamyltransferase; PT – Prothrombin Time; INR – International normalized ratio; PTT - Partial thromboplastin time; WBC – white blood cell; TSH – Thyroid-stimulating hormone; Ref. – Reference; ND – Not detected; Neg. – Negative; ANA – antinuclear antibody; Anti-dsDNA – anti-double-stranded DNA antibody; Anti-RNP – antinuclear ribonucleoprotein antibody; Anti-CENP-B - *anti*-centromere *antibody;* ASMA – anti-smooth muscle antibody; EBV – Epstein Baar virus; CMV – Cytomegalovirus; VDRL – Venereal Disease Research Laboratory; FTA-ABS - fluorescent treponemal antibody absorption test; β-hCG – beta-human chorionic gonadotropin; BEI – biological exposure indice.

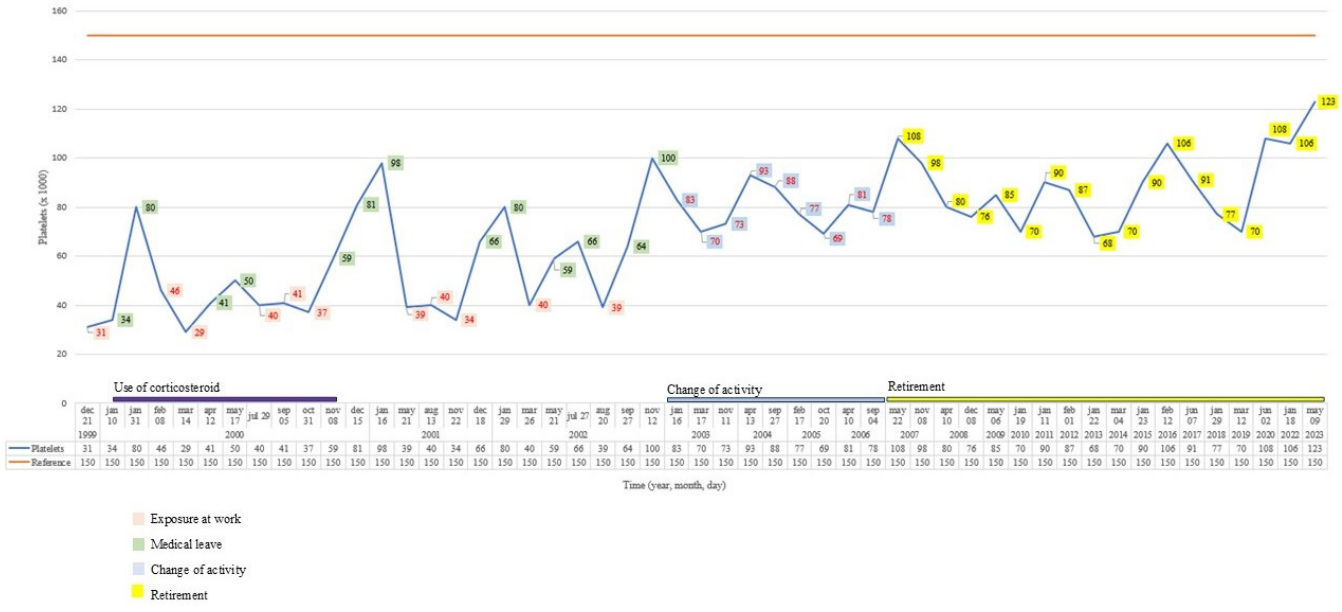

Figure 1. Evolution of platelets count.

DISCUSSION

We present the case of a 34-year-old woman with a history of long-term low-level exposure to toluene in the workplace who was referred to a specialized department for ITP allegedly related to toluene. One particular concern when addressing pathologies related to toluene is its frequent co-exposure to benzene [11]. Even today, with the specifications regarding the purity of toluene, it may contain at least small amounts of benzene [7,8]. Both are highly volatile aromatic hydrocarbons that are predominantly absorbed through inhalation, and their co-exposure alters benzene metabolism and toxicity [11]. Among the systems adversely affected by this co-exposure are the cardiovascular, nervous, reproductive, and respiratory systems [12]. In our case, the diagnosis of hepatitis (data not shown) was probably solely related to toluene exposure based on the investigation carried out and its well-known effects on the liver [5]. On the other hand, the successive drops observed in platelet levels during the course of ITP were probably related to benzene and not toluene, as the benzene is a substance known to be hematotoxic and carcinogenic, and toluene is not [5,11,12]. In both clinical presentations, the results of toluene biomonitoring were within the reference values stipulated by the Brazilian legislation. However, it should be highlighted that these results may be misleading as the material collection occurred at the beginning of the work week. At that time, the ACGIH recommended the analysis of HA-u at the end of the work shift [11].

ITP is the most common cause of isolated thrombocytopenia in healthy individuals, and affects both children and adults. In this report, we present a case of isolated thrombocytopenia with normal physical examination, laboratory data, and peripheral blood smear. Additionally, the patient had the classical features of ITP in adults, with a female predominance. Notably, 80% of newly diagnosed ITP cases are primary, and primary ITP develops into a chronic course in up to 70% of adults [1-3].

Recent research has reported that female sex and a platelet count greater than 20.000 μL are factors that can contribute to a chronic course [4]. Generally, platelet counts tend to fluctuate throughout the disease course and only 11% return to normal levels [13]. In our case, we observed an initial response to a high dose of oral corticosteroids, which has been reported in 70-80% of the cases [1,2]. Thereafter, the platelet count fluctuated in a peculiar pattern, showing a substantial decrease when returning to work and recovering when on medical leave. Given her long-term exposure to toluene and a history of toluene-induced hepatitis, she was referred to the Toxicology Department of a teaching hospital with a suspected diagnosis of toluene-induced thrombocytopenia, a form of drug-induced thrombocytopenia (DITP) [14].

However, when evaluating DITP, two points must be addressed. First, toluene is unlikely to be the cause. Instead, benzene contamination should be considered, as toluene lacks haematotoxic effects, and past reports of such effects were attributed to benzene contamination [5-7]. Before the 1980s, toluene contained considerable amounts of benzene (25%) [6]. Since then, the specifications for the establishment of toluene purity have been published by ASTM [8]. Thus, toluene meeting these specifications may contain approximately 2%–4.5% benzene [7,9]. Although air monitoring indicated low levels of toluene and no analysis for benzene was conducted, the patient's report of an industrial-grade toluene test warrants attention. The results indicated an average boiling range for toluene exceeding the maximum limit by approximately 5ºC, suggesting that benzene constituted roughly 13% of the toluene/benzene mixture used at the facility [7,9]. Consequently, it can be inferred that the patient was exposed to benzene in the workplace.

The second aspect to address is the diagnosis of DITP itself. Benzene appears to be a plausible trigger for ITP due to its hematotoxic effect [5]. However, according to the level of evidence for a causal relationship, DITP seems unlikely because there was no complete or sustained recovery after exposure ceased [14]. Moreover, although the exposure preceded the outcome, there was no characteristic platelet drop within 5–14 days of exposure; instead, it was long-term exposure.

However, the role of benzene as an aggravating agent appears highly probable, as demonstrated by the successive drops in platelet counts after re-exposure to the workplace without adequate protection (Figure 1). Once the patient was definitively removed from the source of exposure, her clinical condition improved and the sudden variations in platelet counts stopped, even though they never normalized, a pattern seen in chronic cases [1,2,13].

We must highlight some points in this report, starting with the need to carry out a thorough diagnostic approach to rule out any cause of ITP, as its treatment may improve platelet count. Common causes such as chronic infection; nutrient deficiencies; pregnancy; recent transfusions and vaccinations; use of drugs other than benzene; hematological conditions; and autoimmune, liver, and thyroid diseases were excluded [1,2,3]. Also, it is a challenge to evaluate cases in which we do not have air monitoring data or access to the workplace. In such situations, it is useful to conduct retrospective exposure profiles based on worker interviews and workplace descriptions [7]. Nevertheless, what draws attention to this is intermittent toluene exposure at work even after diagnosis. One reason for this may be a lack of knowledge regarding toluene contamination. Therefore, raising awareness about frequent contamination of toluene with benzene is crucial, given benzene's hematotoxic properties. Therefore, benzene exposure should be considered in workplaces where toluene is used, and the inclusion of CBC should be recommended for proper health evaluation. Finally, appropriate specifications of the PPE are vital for its purpose. In our case, replacement of the N95 respiratory masks was an urgent measure. Also, biomonitoring procedures, such as the collection time of biological samples, are important. Typically, this occurs at the end of the shift. In our case, urine was collected on Monday after a weekend of rest.

This study had some limitations. First, we had no access

to other workers' health status data, which is one of the instruments used to establish a causal relationship between work and disease. Second, air and biological monitoring of chemicals performed annually in a single measurement may not represent the dynamic levels of exposure [15]. Furthermore, these monitoring methods do not include benzene detection. Third, there was recall bias regarding the brands of toluene vats used. This information allowed us to determine the benzene contents of the labels. Finally, we did not perform drug-dependent anti-platelet antibodies, which is important to confirm the etiology of DITP, because it was not available thereafter.

CONCLUSION

Our case highlights the role of benzene-contaminated toluene in ITP, not as a causal agent but rather as an aggravating agent. Considering the wide use of toluene in many contexts, we recommend that proper health and environmental evaluations should consider benzene exposure in workplaces where toluene is used.

Ethical approval: The project was approved by the Research Ethics Committee of Clementino Fraga Filho University Hospital/UFRJ under Protocol Nº 4.558.938 and CAAE Nº 42653121.2.0000.5257.

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