

# Secondary immune thrombocytopenia supposedly attributable to COVID-19 vaccination

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Accepted 18 April 2021

## SUMMARY

Immune thrombocytopenia (ITP) has been widely reported as a complication of SARS-CoV-2 infection, but to our knowledge, there have been no reports on the association of the COVID-19 vaccine with thrombocytopenia. Here, we report a case of secondary ITP in a patient who was recently immunised with the messenger RNA COVID-19 vaccine BNT162b2 (Pfizer–BioNTech).

## BACKGROUND

There is an ongoing COVID-19 pandemic affecting every country in the world. Over one million people had died from COVID-19 by the beginning of 2021.<sup>1</sup> In Mexico, more than 200 000 deaths have been recorded.<sup>2</sup> This global health crisis has accelerated scientific funding and cooperation; as a result, many vaccines to prevent COVID-19 have been developed.

One of the first vaccines that received emergency use authorisation in many countries was the messenger RNA (mRNA) COVID-19 vaccine BNT162b2 (Pfizer–BioNTech),<sup>3 4</sup> a nucleoside-modified mRNA lipid nanoparticle-formulated vaccine that encodes for SARS-CoV-2 spike protein. Both safety and efficacy have been proven by manufacturer's clinical trials. In regard to reactogenicity, the most commonly reported events have been pain at the injection site, fatigue, headache, chills, muscle pain and fever.<sup>5</sup>

As noted by Berlin, low prevalence adverse events are very unlikely to be identified, even in well-designed phase 3 clinical trials<sup>6</sup>; thus, these kinds of events are often identified through post-market surveillance programmes.<sup>6</sup> The immune thrombocytopenia (ITP) incidence among adults is 3.3 cases per 100 000 adults/year.<sup>7</sup> However, only 37 706 participants received vaccination or placebo and had a follow-up for an average of 2 months in the safety trials.<sup>5</sup>

ITP is an autoimmune disorder in which autoantibodies inhibit platelet production and impair the circulating platelets. Most cases are related to autoimmunity; however, there are secondary trigger conditions, such as viral infections or even vaccines.<sup>8</sup> The present case reports a patient who received the mRNA COVID-19 vaccine BNT162b2 (Pfizer–BioNTech) and subsequently developed secondary ITP.

## CASE PRESENTATION

A 41-year-old woman, with history of multiple allergies (quinolones, cephalosporins, strawberries and iodinated contrast), presented to the emergency department with a 12-hour history of fever, tachycardia and nausea. She had a history of hypothyroidism, hypertension and pre-diabetes and was under treatment with enalapril and levothyroxine. She had received the mRNA COVID-19 vaccine BNT162b2 (Pfizer–BioNTech) 12 hours before the symptoms developed.

At her initial evaluation, the patient reported malaise, headache and loose stools on multiple occasions. She did not report urinary or neurological symptoms. She had taken metoprolol for tachycardia and paracetamol to control the fever. She had not taken any other medications.

A physical examination in the emergency department revealed a blood pressure of 154/99 mm Hg, a pulse of 108 beats per minute and an SpO<sub>2</sub> of 94% breathing ambient air. Her temperature was 37.4°C. She was alert and oriented. She was mildly dehydrated; otherwise, her physical examination was normal.

## INVESTIGATIONS

Initial blood tests showed a normal leucocyte count without lymphopenia; however, moderate thrombocytopenia ( $65 \times 10^9$ ) was remarkably evident. The patient had a previous blood cell count 4 months ago, where platelet count was normal. Coagulation tests, iron levels and storages were normal. Her C reactive protein and IgE were elevated, but otherwise, all tests were within normal range including C3, C4 levels, antinuclear antibodies, anti-Sjögren's-syndrome-related antigen A autoantibodies (anti-SSA), anti-Sjögren syndrome antigen B antibodies (anti-SSB) and anti-DNAbs. The peripheral smear did not show any alterations. The mean platelet volume was slightly elevated 11.3 fL (normal range 6.5–11.0 fL). We did not perform antiplatelet antibodies or bone marrow smear (table 1).

A nasopharyngeal swab for RT-PCR SARS-CoV-2, an SARS-CoV-2 rapid antigen test and an anti-SARS-CoV-2 IgG test were all negative. A CT scan of the lung showed no evidence of infiltrates or areas of ground glass opacities, and an CT of the abdominal was unremarkable.

## TREATMENT

The patient remained in the emergency department, where she was given intravenous fluids



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**To cite:** Fueyo-Rodriguez O, Valente-Acosta B, Jimenez-Soto R, *et al.* *BMJ Case Rep* 2021;**14**:e242220. doi:10.1136/bcr-2021-242220

## Case report

Table 1 Laboratory data

Variable	On admission	18 hours after admission	Fourth day	Day of discharge	Reference range
<b>Blood count cell</b>					
Haemoglobin (g/L)	125	134	119	116	145–185
White cell count ( $\times 10^9/L$ )	6.73	23.5	20.02	16.96	3.5–10.0
Lymphocytes	1.14	2.01	2.59	4.89	1.0–3.5
Platelet count ( $\times 10^9/L$ )	65	39	151	210	150 000–450 000
Creatinine (mg/dL)	0.69	0.69	0.61	0.72	0.74–1.35
<b>Electrolytes</b>					
Sodium (mmol/L)	134.9	137.7	136.6	136.9	135–145
Potassium (mmol/L)	3.9	3.8	3.3	3.8	2.5–5.1
<b>Liver enzymes</b>					
Alanine aminotransferase (U/L)	32		35		0.00–32.0
Aspartate aminotransferase (U/L)	23.4		22		0.00–33.0
Lactate dehydrogenase (U/L)	164		215	176	122–222
Total bilirubin (mg/dL)	0.36		0.23		0.10–1.20
Direct bilirubin (mg/dL)	0.15		0.09		0.00–0.30
Indirect bilirubin (mg/dL)	0.21		0.14		0.00–1.00
C reactive protein (mg/dL)	8.05	5.69	1.91	0.72	0.00–0.50
IgE (U/mL)			259		0.00–100

therapy, analgesic and antipyretic management with paracetamol. After 12 hours in the emergency department, a new blood test revealed a decrease in platelets ( $38 \times 10^9$ ). At that point, she developed headache, bleeding gums and petechiae, so we administered 1 gm of methylprednisolone. A CT scan of the brain was performed without evidence of intracerebral haemorrhage. Haematology was consulted for suspicion of secondary ITP due to the COVID-19 vaccine. We started targeted treatment with 40 mg intravenous dexamethasone daily and intravenous immune globulin (IG) calculated per kilogram of weight (a total dose of 24 gm) according to the 2019 international consensus on the investigation and management of primary ITP.<sup>9</sup>

### OUTCOME AND FOLLOW-UP

After the first dose of intravenous IG, she presented mild hypertension, so amlodipine was started. She was then admitted to the internal medicine ward for clinical surveillance. After the second dose of dexamethasone and intravenous IG, platelet count began to increase and gingival haemorrhage resolved. She received a total of four doses of dexamethasone and three doses of intravenous IG. Platelet count remained in the normal range, so we were able to discharge her after 5 days. We followed up with an external consultation a week later, where we evidenced a platelet count of  $629 \times 10^9$ .

### DISCUSSION

Many autoimmune effects have been related to vaccines, including type 1 diabetes mellitus, multiple sclerosis, Guillain-Barre syndrome and acute disseminated encephalomyelitis.<sup>8</sup> However, ITP following vaccination has been previously reported in the literature, specifically with measles, mumps and rubella vaccine. Recently, a COVID-19 vaccination-related ITP case has been reported.<sup>10</sup> For most of the cases, a temporal relation has been established, nevertheless, we do not suggest that these findings nor our case have a causative association with the vaccination. There are biological mechanisms that could explain ITP clinical findings that should be explored too, but the aim of this case report is not to establish causation,<sup>11</sup> but to describe our findings and raise awareness for clinical and surveillance purposes.

ITP is an autoimmune disorder in which autoantibodies inhibit platelet production and impair circulating platelets, resulting in thrombocytopenia that is not associated with other haematologic abnormalities.<sup>12</sup> Most cases are related to autoimmunity; however, there are secondary trigger conditions, such as viral infections or vaccines. The main mechanism is of immune origin through the cross-reaction of platelet antibodies with platelet antigens, such as GP Ib/IX, GP Ia/IIa and GP VI.<sup>8 12 13</sup> Therefore, there are other antigen responses to vaccine constituents, adjuvants and preservatives<sup>8</sup> or by molecular mimicry, epitope spreading and polyclonal activation.<sup>14</sup>

Reactions can occur shortly after exposure to a trigger. For instance, if the patient has been sensitised by previous exposure to the drug, the onset of thrombocytopenia may be more rapid (eg, as early as hours after exposure).<sup>15</sup> In our case, the patient developed thrombocytopenia in 48 hours, and it is unlikely that previous exposure to the vaccine constituents or adjuvants was involved particularly in our case because it was the vaccine's first dose, and the patient has no history of COVID-19 infection.

Complications related to this entity might be life-threatening when the platelet count is below  $5 \times 10^9$ . In contrast, in our patient, the lowest platelet count was  $39 \times 10^9$ . Therefore, the clinical manifestations of our patient were mild, only with mucocutaneous bleeding. Consequently, the outcome was successful after prompt diagnosis, ITP and treatment with glucocorticoids and intravenous IG.

COVID-19 has been linked to ITP. For instance, in September 2020, Bhattacharjee wrote a systemic review of 45 patients with COVID-19-related ITP.<sup>16</sup> Still, only two cases of this possible association between COVID-19 vaccination and ITP have been reported, one in a medical journal<sup>9</sup> and another in the press.<sup>17</sup>

Vaccines are among the most important inventions in science history and as any other pharmaceutical product should comply with postmarket regulations, including the design and operation of postmarket surveillance systems.<sup>18</sup> In México, the federal government has established a protocol for the report of Events Supposedly Attributable to Vaccination or Immunization (ESAVI) and our case has been

reported as a severe ESAVI according to the national regulations,<sup>19</sup> further investigation is needed in order to establish if ITP is or not associated with the vaccine. Moreover, ITP onset after receiving a vaccine may not be a reason to discourage the vaccination, since it is a previously reported phenomenon. Nevertheless, there should be caution in patients with previous ITP.

### Learning points

- ▶ Secondary immune thrombocytopenia can be associated with the COVID-19 RNA vaccine.
- ▶ Immune thrombocytopenia (ITP) should not be a reason to discourage vaccination against SARS-CoV-2.
- ▶ Although ITP following other vaccines has been previously reported, we still do not know the incidence of such adverse reaction linked to messenger RNA COVID-19 vaccine BNT162b2 (Pfizer–BioNTech).

**Acknowledgements** We acknowledge Miss. Olivia Gonzalez for English proofreading support.

**Contributors** BV-A, OF-R and RJ-S conceived the idea and design of the article. OF-R, RJ-S, YN-Y, SIA, RTG, MAGS and BV-A contributed to the preparation and review of the initial manuscript. BV-A drafted the final work and reviewed it critically. All authors approved the final version.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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