Isolated thrombosis after COVID-19 vaccination: case series

Mona Al-Ahmad¹,2 · Mona Al Rasheed³ · Lulwa Altourah³ · Tito Rodriguez-Bouza⁴ · Neveen Shalaby³

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Abstract
Background Data regarding thrombosis after COVID-19 vaccination are scarce.
Methods Clinical and laboratory data were collected from all patients who developed thrombosis within 4 weeks of receiving the Pfizer or Oxford/AstraZeneca vaccine. None had a COVID-19-positive swab.
Results Seventeen patients were included, with average age of 48.8 years and equal proportion of females to males. Our data suggest that thrombosis occurred in 1 in 163,000 of all individuals who had received any dose of any type of COVID-19 vaccine: six (1 in 123,000) patients after the first dose of Oxford/AstraZeneca, none after the second dose of Oxford/AstraZeneca, four (1 in 257,000) patients after the first dose of the Pfizer vaccine, and seven (1 in 102,000) patients after the second dose of Pfizer vaccine. Three of 17 patients with thrombosis (17.6%) died.
Conclusions We believe this report to be one of the earliest in the literature to address the question of whether isolated thrombosis is a possible complication of COVID-19 vaccination.

Keywords COVID-19 · Thrombosis · Vaccine

Introduction
SARS-CoV-2 was linked to an increased risk of thrombosis both during the active and post-infective period [1–3]. Several guidelines have been published addressing management of this possibly lethal complication [4, 5]. In Kuwait, the two available vaccines are Pfizer-BioNTech, and Oxford/AstraZeneca and to the time of preparing this report, over one and half million people were vaccinated [6]. However, a few serious complications were brought to attention, including several reported thrombosis cases; this raised the question of whether a valid link is present between the vaccine and the thrombosis incidences.

Methods
We conducted a single-country case-report series with all patients reported with thrombosis on the first 4 weeks after vaccination. Data were taken from January 2021 to 24th of July 2021. For each patient, we recorded age, gender, previous medical health (PMH), baseline aspirin/anticoagulation, COVID-19 nasopharyngeal PCR swab, type of vaccine, dose of vaccine (1st or 2nd), type of thrombosis, location of thrombosis, time between vaccine and onset of symptoms, nadir platelet count, d-Dimer, fibrinogen level, lupus anticoagulant, anticardiolipin (ACL), beta-2-glycoprotein (B2GP), thrombophilia screening, heparin-induced thrombocytopenia and thrombosis (HITT) ELISA assay, treatment outcome, and additional description of the case.

Results
From January 2021 till 24th July 2021, a total of 1,745,713 patients had received Pfizer vaccine in Kuwait; of these, 1,029,417 had received the first dose only and 716,296 had received both doses of the vaccine. In contrast, a total of 1,025,715 had received Oxford/AstraZeneca vaccine. Of these, 736,123 had received the first dose only and 289,592
had received both doses of the vaccine. The first case of thrombosis was reported on the 22nd February 2021.

In this article, we are reporting a total number of 17 patients who had developed thrombosis after receiving COVID-19 vaccination which represents 1 in 163,000 of all individuals who had received any type or dose of the COVID-19 vaccine. Of these, 6 patients had developed thrombosis after the first dose of Oxford/AstraZeneca vaccine which represents 1 in 123,000 among all individuals who had received the first dose of Oxford/AstraZeneca vaccine in Kuwait. We did not encounter any case of thrombosis after the second dose of Oxford/AstraZeneca vaccine (Table 1).

Of the patient who developed thrombosis after Pfizer vaccine, 7 out of 11 developed the thrombosis after the second dose of the vaccine which represents 1 in 102,000 of all individuals who received the second dose of Pfizer vaccine. Four out of eleven developed thrombosis after the first dose of the Pfizer vaccine which represents 1 in 257,000 of all individuals who had received the first dose only of the Pfizer vaccine (Table 1).

Clinical characteristics, laboratory results, and management of cases are summarized in Table 1. Equal number of females to males had developed thrombosis in patient who received Oxford/AstraZeneca vaccine, in contrast to, 5 out of 11 females who had developed thrombosis in patient who had received Pfizer vaccine. Regarding previous management, only one patient was on aspirin and none were on long-term anticoagulation. Ten patients had venous thrombosis [Deep vein thrombosis (DVT)/Pulmonary embolism (PE) and two patients with cerebral venous thrombosis (CVT) (59%)] and seven out of seventeen patients had developed arterial thrombosis [myocardial infarct (MI), cerebrovascular accident (CVA), Peripheral vascular disease (PVD) (41%)]. There was one patient who developed both arterial and venous thrombosis. In patients who received Pfizer vaccine, 9 out of 11 (82%) developed venous thrombosis and 2 out of 11 (18%) developed arterial thrombosis. In patients who received Oxford/AstraZeneca vaccine, 2 out of 6 (33.3%) developed venous thrombosis compared to 4 out of 6 (66.6%) who developed arterial thrombosis. The mean time between vaccine exposure and the thrombosis is 13 days with a median of 14 days and a range of 25 days (1–26 days.). All patients had COVID-19 nasopharyngeal PCR negative swab. Two patients only had thrombosis with thrombocytopenia, one was after the first dose of the Oxford/AstraZeneca vaccination and the other one was after 2nd dose of Pfizer vaccine, which may represent the first case of Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) after Pfizer vaccine. In the first case, hematology service was not consulted and HITT assay was not sent, while in the second case, HITT assay was sent, but the reagent was not available. There was one patient who developed massive CVA, and she had very high d-Dimer but no thrombocytopenia (complete blood cell (CBC) analysis on admission was normal, with no subsequent CBC). This case can be considered as suspected cases of VITT. HITT assay was sent, but the reagent was not available. Seven patients had thrombophilia screening done. Four of those had lupus anticoagulant positive (repeated twice 3 months apart) with negative ACL and B2GP, and one had borderline low protein S level, while the rest had negative thrombophilia screening. Three out of the seventeen patient had passed away. All the three-patient had arterial rather than venous thrombosis. Two patients had received the first dose of Oxford/AstraZeneca vaccine and one had received the second dose of Pfizer vaccine. Two of those patients had very high d-Dimer in addition to thrombocytopenia and one had very high d-Dimer without thrombocytopenia which can potentially represent suspected cases of VITT. Unfortunately, HIT assays were not sent or not available for any of these patients to confirm possibility of VITT.

Discussion

The emergency release of the Pfizer vaccine was in December 11th 2020 and of Oxford/AstraZeneca was on March 17th 2021 [7, 8]. Thrombosis has not been described as a possible vaccine complication in initial clinical trials [7, 9]; however, there has not been any case reports or case series in the literature linking thrombosis to vaccination except those describing VITT [10–13]. A safety report published by health product regulatory authority stated that a few cases developed thrombosis; however, those patients already had risk factors for such complication [14]. Another paper collecting data from Vigibase, a Sweden databank used to gather information about adverse drug reactions, stated that thrombosis has been reported post-vaccination; nevertheless, a comparison between vaccinated and unvaccinated individuals is needed to determine a true association. In this article, both arterial and venous thrombosis has been reported, including unusual site thrombosis, such as cerebral vein thrombosis, similar to our reported cases. People vaccinated with mRNA-based vaccine (e.g., Pfizer/BioNtech) showed more venous than arterial thrombosis compared to those vaccinated by Oxford/AstraZeneca who had equal number of arterial and venous thrombosis. Thrombocytopenia associated with positive HIT assay, disseminated intravascular coagulation, and positive antiphospholipid antibodies were also reported in patients who received COVID-19 vaccines [15].

A recent publication [16] showed an association between the first dose of Oxford/AstraZeneca vaccine and arterial thrombosis. No similar association was found between Oxford/AstraZeneca vaccine and venous thrombosis nor Pfizer vaccine with arterial or venous thrombosis. In our
Table 1 Clinical characteristics, laboratory results, and management of cases

| Vaccine               | Pfizer 1st dose | Pfizer 2nd dose | Oxford/AstraZeneca 1st dose |
|-----------------------|----------------|-----------------|----------------------------|
| Age, average (SD)     | 39.5 (18.4)    | 58.9 (15.8)     | 43.3 (8.3)                 |
| Gender                |                |                 |                            |
| Female                | 2              | 3               | 3                          |
| Male                  | 2              | 4               | 3                          |
| PMH                   |                |                 |                            |
| Healthy               | 2              | 4               | 5                          |
| DVT/PE                | 1              | 0               | 0                          |
| DM + smoker           | 0              | 0               | 1                          |
| DM + HTA              | 1              | 3               | 0                          |
| Thrombotic events in relation to individuals received vaccine | | | |
| Total: 1/163,000      | 1/257,000      | 1/102,000       | 1/123,000                  |
| Type of thrombosis    |                |                 |                            |
| Venous                | 3              | 3               | 2                          |
| Arterial              | 1              | 3               | 4                          |
| Both                  | 0              | 1               | 0                          |
| Location of thrombosis|                |                 |                            |
| PE                    | 1              | 1               | 0                          |
| DVT                   | 1              | 2               | 0                          |
| Cardiac               | 0              | 1               | 1                          |
| CVA                   | 0              | 1               | 3                          |
| CVT                   | 0              | 1               | 1                          |
| Limbs                 | 1              | 0               | 0                          |
| DVT + PE              | 1              | 0               | 1                          |
| DVT + CVA             | 0              | 1               | 0                          |
| Average days from vaccine to symptoms (SD) | 13 (5.7) | 14.3 (8.5) | 13.5 (5.8) |
| Nadir platelet (x10^9/L) | 262 (85.1) | 262 (104.9)    | 280.8 (130.5)              |
| D-Dimer (ng/ml DDU)   | 1542 (1236.6)  | 706.5 (598)     | 3125 (3283.9)              |
| Thrombocytopenia or very high D-Dimer | 0 | 1 | 2 |
| Fibrinogen (g/l)      | 2.6 (0.5)      | 2.9 (1.5)       | 2.7 (0.7)                  |
| Lupus anticoagulant\* Positive | 3/3 (100%) | 1/4 (25%) | n.d |
| ACL\* Positive        | 0/3 (0%)       | 0/4 (0%)        | n.d                        |
| B2GP\* Positive       | 0/3 (0%)       | 0/4 (0%)        | n.d                        |
| Thrombophilia screen\* Positive | 0/3 (0%) | 0/2 (50%) | n.d |
| HIT ELISA assay\*     | n.d            | n.d             | n.d                        |
| Treatment             |                |                 |                            |
| Rivaroxaban           | 0              | 1               | 1                          |
| LMWH + warfarin       | 3              | 2               | 1                          |
| Heparin + rivaroxaban | 1              | 1               | 0                          |
| LMW + rivaroxaban     | 0              | 1               | 0                          |
| ASA + rosuvastatin    | 0              | 0               | 2                          |
| ASA + heparin + bivalrudin + IVIG | 0 | 1 | 0 |
| None/not available    | 0              | 1               | 2                          |
| Outcome               |                |                 |                            |
| Stable                | 4              | 6               | 4                          |
| Passed away           | 0              | 1               | 2                          |

DVT deep vein thrombosis, PE pulmonary embolism, UL upper limb, CVA cerebrovascular accident, CVT cerebral venous thrombosis. ACL anticardiolipin antibody, B2GP beta2 glycoprotein, HIT assay heparin-
case series, all patients who developed thrombosis after Oxford/AstraZeneca vaccine did so after the first dose of the vaccine which was consistent with findings from the previous study.

In conclusion, isolated thrombosis was not reported as one of the vaccines adverse events in the earliest vaccine randomized controlled trials [9, 17]. However, several other adverse events were also reported post emergency release of the vaccine such as VITT [10–13]. A true link between our reported isolated thrombosis cases and the vaccine is yet to be established by a large cohort study. If a true link was to be established, the mechanism by which the vaccine plays a role in causing thrombosis is unclear. Whether it affects any aspect of Virchow’s triad: hypercoagulability, stasis, or vascular endothelia damage or has a new undiscovered mechanism is yet to be proven [18]. However, since thrombosis is possibly fatal, reporting such incidences could raise awareness and start an investigation searching for true link between the two events. We believe this report to be one of the earliest in the literature to address the question of whether isolated thrombosis is a possible complication of COVID-19 vaccine, the specific type of the vaccine causing the thrombosis and whether thrombosis occurs after the first or the second dose of the vaccine.

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Author’s contribution MA and MA initiated and coordinated the development of the paper, and worked on data collection, analysis, and writing up the paper. MA, MA, LA, TR, and NS analyzed and interpreted the results and helped in writing up introduction. All authors read and approved the final manuscript.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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Table 1 (continued) induced thrombotic thrombocytopenia assay, LMWH low-molecular-weight heparin, IVIG intravenous gammaglobulin, n.d. Not done

aNumbers are expressed as the positive results among those who made the test
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