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Case Report

### THROMBOCYTOPENIA AND ITS ASSOCIATED ISSUES INCLUDING ISCHEMIC STROKES, CLOTS AND BLEEDING REPORTS IN DIFFERENT COUNTRIES IN PATIENTS WHO NEWLY GET ADENOVIRAL VECTOR-BASED COVID-19 VACCINE

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**Abstract:**

*Here we are elaborating the cases of a rare reaction of COVID-19 vaccine based on adenoviral (ChAdOx1) vector, the reactions include thrombocytopenia (low level of platelets count), rare type of blood clots, and ischemic strokes. The cases describe first a Pakistani 55 years old man who was hypertensive and diagnosed MI before 3 years, was on different medication, took first shot of vaccine (AZD1222) and felt little weakness including headache, after 3<sup>rd</sup> day of shot a greater elevation in blood pressure was seen, later he fell unconscious and later on computer tomography scan on head showed clots in right hemisphere with acute cerebral edema, the patient was completely paralyzed on the left size, in the blood reports there was a rapid decline in platelets count from 110000 to 65000 per uL, patient had 2 cardiac strokes events on 7<sup>th</sup> day of hospitalization with 2<sup>nd</sup> cardiac stroke he passed away, with CT scan it showed clots in both hemisphere, and blood reports showed platelet factor (PE-4) reactive antibody, here we took a reference of Danish 60 years old woman who was diagnosed with same kind of events after receiving same vaccine first shot, she passed away on 6<sup>th</sup> day of hospitalization. Her CT scan and MRI scan also showed acute cerebral edema, and blood reports revealed platelet factor (PF-4) reactive antibody, many countries also reported such cases, but no detailed information was provided. This can be novel immune response against specific type of vaccine, need to be evaluated further.*

**Keywords:** Thrombocytopenia, Hemorrhage, Stroke, antibodies, vector, vaccines

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**INTRODUCTION:**

Coronavirus is from a group of RNA viruses (single strand), they cause infection in mammals and birds, new strain infect human than other species, mostly cause respiratory tract infection, among that six coronaviruses have been known to infect human hosts and cause severe respiratory diseases, among the diseases the severe one are severe acute respiratory syndrome also called (SARS-COV) which is diagnosed mostly in recent cases and Middle East respiratory syndrome coronaviruses (MERS-COV), this viruses of this family are highly pathogenic and host in humans that cause worldwide outbreak.[1-4]

The morphology of corona viruses is very specific and distinctive, as the name describe the name corona an outer finger, coronal of embedded envelope protein, these viruses, causing broad spectrum respiratory infections.

Since the first case of corona virus reported on 31 December 2019 in Wuhan, China, its origin was big controversy between worldwide, various speculation were in the world about the virus either it is transmitted from a natural source or it is developed by humans in laboratory, so the outbreak of the this virus spread worldwide.[16]

Then scientist from worldwide rushed into the development of vaccine, since the various strains also discovered, causing mire catastrophic effects, resulted in extensively study on SARS-CoV-2's genome every carried on. Researchers at the University of Bologna drew from the analysis of 48,635 corona viruses' genomes, these genomes were isolated by the researchers in the labs worldwide. Among those different strains were more persisted in different region as Strain G and strain GR were most frequent in Europe, In North America GH strain was most frequent while in the South America region GR strain were found, In Asia Wuhan L strain were present later G and GR strain were increasing also.

The genome prepared helped scientist for the development of vaccine, after the GISAID shared the genetic sequence data of SARS-CoV-2, the pharmaceutical industries all over the world announced their interest and major commitment to address COVID-19 infection and for the preparation of vaccine.

In the last phase of trials many COVID-19 vaccines were considered beneficial as much as 95% to 96% in preventing morbidity due to recent COVID-19 pandemic. Almost Twenty vaccines are authorized yet by at least one local or national authority of different countries for public use: Among that are 2 RNA vaccines of Pfizer and Moderna), 9 are conventionally inactivated virus vaccine were prepared ( Chinese Academy of Medical Sciences, Minhai-Kangtai, Covaxin, CoviVac, QazVac, BBIBP CorV, CoronaVac and WIBO CorV, coVIran Barkat), and the viral vaccines were prepared on adenoviral vector based are 5 including (Oxford–AstraZeneca, Convidecia, Sputnik V, sputnik light and Johnsons & Jhonsons ), and four protein subunit vaccine (EpiVacCorona, MVC-COV1901, Soberana 02,zf2001, and Abdala).

Among them viral vector vaccine reported some reactions like blood clots and bleeding, first in the month of march 2021 related to AstraZeneca COVID-19 vaccine, till June 2021, 300 confirmed cases were reported lined to AstraZeneca COVID-19 vaccine, later Johnsons and Johnsons vaccine in United Kingdom and USA.

The safe administration of the vaccines was and still is of major concerns to prevent more mortality rate because to COVID-19 virus and for the bringing back of normal healthy life. But rare thrombotic events related to the ChadOx1 nCOV-19 vaccine, and the possibility of specific immune response include thrombocytopenia which is immune mediated as mentioned by Norwegian researchers among USA and UK researchers. [5-6]

Here, we are describing a Danish case among the some other cases Pakistan, where people diagnosed with adrenal hemorrhages and acute ischemic stroke, when blood samples were send to laboratory the results showed rapid fall in platelet counts. The sepatients were positive for platelet factor-4 (PF 4) antibodies too. First, we need to describe, [1-6]



**Figure. 1**

In he beginning of the noval covid-19 pandemic, blood clotting was reported as a side effect of SARS-CoV-2 virus by many countries especially in elderly patients and later reported as a rare side effect (one in millions) of some vaccines usually based on adenoviral vector vaccine.[13]

#### **The Site of Blood clot**

In the deep veins when a blood clot forms called deep venous thrombosis (DVT), most likely in the leg lower area, in the veins of thigh, or in pelvis area as their is low velocity and high pool of blood. After the formation blood clot, it brake into small fragments and these fragments travel into small narrow veins and arteries and can block one of the arteries in the lungs which is called pulmonary embolism (PE). This happen in very rare conditions but can be risky, but these clots are preventable and dissolvable if the diseased diagnosed early. In the U.S only every year, about one million people diagnosed with blood clots and among them 100,000 people die from blood clots.[11]

#### **The connection between blood clots and vaccines**

Among all vaccines the clots are only linked to the AstraZeneca and Johnsons & Johnsons vaccines have particular characteristics of both using adenovirus

#### **Defining a Blood Clot.**

Blood clot is described as a aggregation of blood cells usually platelets and proteins (coagulative proteins) that form a clumpy mass together, forming a gelly substance that can obstruct flow of blood. In normal conditions blood clots are often seen in certain conditions such as injuries, trauma, surgeries, or infections to maintain homeostasis. [9]

vector: these clots are found in rare body parts such as brain or abdomen, with them low levels of platelets found in all reported cases, platelets are blood cell that help in blood coagulation. On performing further analysis it was found that there was a condition called heparin induced thrombocytopenia abbreviated as HIT also associated with these conditions , it is a rare side effect noted sometimes in those people who are administered with the anti-coagulant heparin for a long period , in the reported cases in this article both patients did not take that drug.[10]

HIT is activated( triggered) when heparin molecule binds with a protein called platelet factor usually called factor 4. This mechanism initiate an immune response which resulted in the production of antibodies against this factor, which ultimately results in platelet cell death by destructing it, by this the dying platelet release clot promoting material. [11-12]

Both AstraZeneca and J&J using adenoviruses as a vector, which carry the fragments of DNA codone for encoding of a coronavirus protein usually called spike proteins in humans. In the cells's protein forming machinery then uses this DNA to make the spike proteins which then activate immune responses against the viruses.

At present, the researchers working on it don't know the exact mechanism of these events and what is the main component of these vaccines is causing this immune response against platelet factor. "It can be caused by the vectors used in vaccine, or it can be caused by the spike protein, it can be caused by a contaminant present in the vector," says by most viral immunologist who worked on this. [13-15]

#### **Only Adenoviruses vaccine or other vaccines are also responsible for blood clotting?**

The vaccines prepared by Oxford-AstraZeneca and Johnsons & Johnsons are different vaccines as they have different adenoviruses as a vector, but the reaction appearance of the HIT and the symptoms among recipients of both vaccines are almost same, no reaction of a HIT-like response was reported among the people who received different type of vaccine, based on mRNA, so this has raised concerns about the problem is due to adenoviruses being used as a vector in these vaccines. Another vaccine called Sputnik V rely on adenoviruses is developed in Moscow by the Gamaleya Center of Epidemiology and Microbiology.

In a report, Gamaleya described that Sputnik V vaccine is from the other adenoviral vector. In the statement they mentioned "All vaccines based on adenoviral vector platform are different and not directly comparable" so pointing that the virus cells in which they were produced were different. also, they mentioned that there is difference in the sequence of the DNA they carry which encode spikes proteins, and the methods of purifying them are also different, and the dosage at which they are administered are also different.

So the most important point in recent days is the identification of a component that trigger the response is important for future vaccines, he said. Should we rely on adenovirus vaccines or we should rely more on mRNA vaccines in future?" he says. "That will be a big concern for the near future."

To check that a Virologist at Erasmus University Medical Center in Rotterdam named Eric van Gorp in the Netherlands, is managing a team, they will look at the different vaccines's effects on vascular, that are grown in the laboratory. The group of scientist will also look for antibodies produced against platelet

factor 4 which are produced due to different COVID-19 vaccines. But yet they have to place their studies in front of world. [17-21]

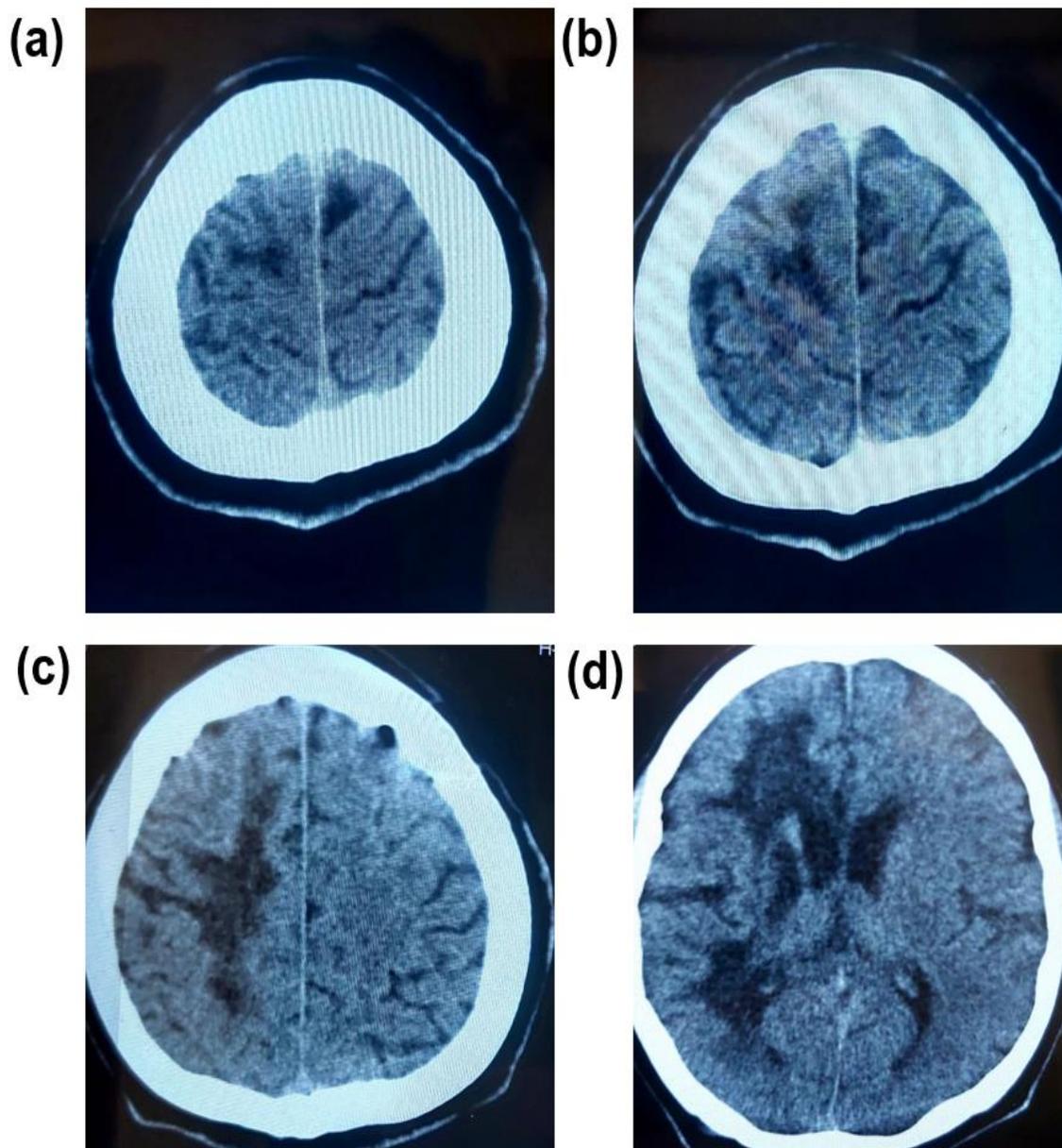
#### **CASE REPORTS:**

In Pakistan, several cases were reported in Pakistan, but exact figure is not available, especially the elderly people who received earlier vaccine based on adenoviruses vector as many physicians doubted the clot formation in the people received recent vaccine. A man aging 54 years died just after arriving in Pakistan from a Gulf country where he received a dose of Oxford-astraZeneca vaccine, but no evaluations were performed, neither studies were performed. But this case was later studied by us, showing this man was suffered with hypertension and angina from last 5 years was on nitroglycerine, aspirin 75mg, simvastatin 40mg, amlodipine and valsartan in combination 5mg and 160mg twice.

He received his first dose of (AZD1222) and he was fine later on 3<sup>rd</sup> day he was hypertensive and felt angina pain, after a while he fell unconscious, and brought to hospital where doctor tried but he couldn't gain consciousness, then computer tomography scan were performed and clots were found in one hemisphere and cerebral edema was found, later patient was in partial senses with left side complete paralyzed.

Blood test performed, and reports showed fall in platelets count from 110000 to 6500 uL, in initial days patient didn't receive any platelet pool, but after first cardiac arrest he was given 3 pools of platelets. The patient then brought back to Pakistan where he got his first stroke and then again computer tomography scan were performed found clots in both hemisphere with cerebral edema but no ischemic or hemorrhage lesions were found also in his case and then patient went on ventilator support after day with second heart stroke he passed away.

The reporting of such cases in Pakistan is very rare because of almost no follow up of patient and lower investigating approach of physicians and lack of resources. No such cases is yet officially reported by other vaccines such sinopharm vaccine and sinovac vaccine.



**Figure 2: showing**

Neuroimaging(computer tomography scan, CT scan and magnetic resonance imaging, MRI scan) A and B= To the right: axial, diffusion imaging on magnetic resonance imaging demonstrating a right middle cerebral artery infarction. C and D To the left: axial, nonenhanced computer tomography demonstrating right middle cerebral artery infarction, cerebral edema.

**Table 1: showing the results of lab reports taken on different days while patient was hospitalized.**

	Day 1 of hospitalization	Day 2	Day 5	Day 7 the death date	Normal range
C protein reactive mg/L	2.6	156	206	78	< 8.0
Pro-calcitonin µg/L			0.33	0.17	< 0.5
white cell count per micro litter	10,800	7,900	6,100	4,900	3,400-10,000
lymphocyte count per micro litter	960	1,480	1,030	800	1,300-3,500
neutrophil count per micro litter	9,400	5,210	4,530	3,960	3,960
potassium mmol/L	3.3	3.4	3.5	4.0	3.5-4.6
hemoglobin g/dL	14.0	13.7	12.9	8.4	11.7 – 15.2
monocyte count per micro litter	580	620	390	690	200-700
platelet count per micro litter	110,000	48,500	23,500	6,500	165,000 - 400,000
antithrombin IU/mL		0.80	0.59	0.8	0.8 -1.2
CT EXTEM (sec) b			78		< 74
CT ENTEM (sec) b			144		< 121
fibtem A10 (mm) b			14		> 8
lactic acid mg/dL	15.06	7.60	6.60	6.81	4.5 - 22.0
creatinine mg/dL	0.70	1.15	1.00	1.02	0.50 - 1.02

Such similar and most briefed case is reported in Denmark, that case describes a 60-years elderly woman with previous medical history majorly of Hashimoto thyroiditis and hypertension. The lady was taking losartan 50 miligram daily as antihypertensive, simvastatin 40 miligram as lipid lowering agent and levothyroxine 50/100 microgram not daily but on day after day for the mentioned diseases. The lady got her 1st dose of AstraZeneca vaccine and suffered with a mild headache on the next days. This patient then admitted to hospital on the 7th day of vaccination with pungent, convulsive, persistent abdominal pain. Urine samples were sent to laboratory for analysis made and it was +ve for blood. After that a scan called Computer Tomography (CT) of the whole abdomen was performed, that showed bilateral adrenal hemorrhage and subcapsular renal hematoma. This condition was rare doctors took the complete history of previous week and even before vaccine, but nothing suspicious was found. The patient went into coma state in following days.

Blood tests as showed in table given by hospital a surprisingly drop in platelet count and the patient was administered with total three pools of platelet concentrates by external source before the procedure of hemicraniectomy. During her total stay in hospital, the lady was administered a total seven pools of platelet concentrates. After that her hemicraniectomy was performed, but unfortunately the lady didn't

recover and didn't regain her consciousness and remain unconscious. After operative procedure dalteparin 5000 IU daily was administered later. On the 4th day at hospital, first three fingers tips later full 3 fingers of the left hand were turned blue. After that the skin of the left foot was mottled as decreased in capillary response to the skin. On next CT scan of the cerebrum were performed and it showed edema of the right hemisphere but no new ischemic or hemorrhagic lesions were found but an unresolved midline shift was seen. Later that the lady was transferred to palliative care with the willing of family, and the patient passed away on the 6th hospital day.

#### In USA

As the first case of blood clotting was reported in march but in April, the regulators in United States urged healthcare professionals to put temporarily ban on administering vaccine made by Johnson & Johnson of New Brunswick in New jersey, because there were reports of 5 to 6 suspected cases of rare form of blood clotting among the nearly 7000000 people who got the vaccine.

This ban came because first European regulatory authorities showed their concerns about a suspected link between these unusual blood clots and the Oxford–AstraZeneca vaccine, developed by AstraZeneca in Cambridge with the collaboration of University of Oxford in the United Kingdom.

**In India**

Adverse effect committee of India reported almost 500 cases of side effects following the injection shot of an imported vaccine exact names were not given, the ministry said that among them 26 of which were potentially thromboembolic (the formation of a clot in a blood vessel that might break loose and cause clumping of another vessel), the nature of clots were not given, the committee described that they didn't receive any information about clot related reactions after the use of regionally developed Covaxin vaccine, which has been given in throughout India.[16]

**In United Kingdom**

Till now 30 cases of rare blood clot events due to vaccine have been identified after the use of the AstraZeneca COVID-19 vaccine only according to British agency, including 5 of the cases the agency previously reported.

The Medicines and Healthcare products Regulatory Agency a British regulatory authority said it had received no such reports of clotting events for the use of the vaccine made by BioNTech SE and Pfizer Inc. The nature of clots and patient detail in these cases were also not described by ministry.[13]

**DISCUSSION:**

A vaccine is prepared biologically that provide active immunity to a particular infectious disease, vaccine contains agents that resemble the disease causing microorganisms and it is made from weakened/attenuated or killed forms of the microbe, its toxins, or either of its surface proteins.

As a vaccine activates the immune system so it have many adverse effects too. Most common side effects that are reported include pain and swelling at the site of injection, mild to moderately headache, pain in muscles and feeling unwell. Very rarely, but an autoimmune disease can be elicited as immune reactions occur such as, with vasodilation and hypotension due to anaphylactic shock is the most rare but fearful if happen and treatment should be life-saving.

In above discussed cases as one reported in Denmark several differential diagnoses were considered. Including blood cultures were performed considering several similar conditions as endocarditis both infectious and non-infectious was unlikely, and sample gave normal blood cultures and echocardiography of transthoracic area was performed. Septicemia and in particular adrenal hemorrhages with Waterhouse Friedrichsen syndrome as meningococcal disease can be its cause was also

unlikely, gave normal blood culture and neisseria meningitidis antibody negative for cerebral edema. later Aortic dissection were performed.[7-12]

Because clots in these patients were of different shapes, Catastrophic antiphospholipid syndrome was considered, giving the negative tests for cardiolipin antibodies, beta2-glycoprotein1 and lupus anticoagulant. The picture could be similar to disseminated intravascular coagulation, but the biochemical pattern observed was not compatible with this as changes were noted in activated b antithrombin, partial thromboplastin time (APTT), but they were unpredictable.[1-7]

In all other cases especially the one in Pakistan reported was not studied in detail and no dissection was performed but the sample of blood was taken and send to laboratories and found that these clots were different from the normal clots, like found in previous case, clots in brain were found very rarely, but as reported in Denmark this patients also showed clots in both hemispheres, no such evaluation were made in other countries, countries like India and Pakistan where a large proportion of elderly population are already hypertensive with MI, coronary artery blockage and kidney problem, reports on these type of cases are rare, as well the other factor is these country didn't receive of Oxford-AstraZeneca vaccine initially, later in a very small proportion.

**CONCLUSION:**

Here we presented different cases of thrombocytopenia, ischemic stroke and rare blood clots were found in the patients who received a shot of adenoviral vector based vaccine, computer tomographic and magnetic resonance imaging scan were performed which showed rare blood clots and cerebral edema, blood reports showed thrombocytopenia and presence of platelet factor (PF-4) reactive antibody, as these studies are performed at small scale, so we suggest special guidelines should be made all around the worldwide to report such cases and these events should be evaluated on professional bases before setting any statement about vaccine, as these cases are rare one in millions.

**Declarations:****Consent**

Consent of this publication of neuroimaging scans was taken from the patient's relatives.

**Disclosure**

The reports of the Pakistani patient were sent to different doctors for professional opinion including Dr

Majid from King Edward Medical University Lahore, Pakistan. Dr. Wasif Altaf a doctor from Multan Pakistan. Doctor Zayoda Aktamovna from Tashkent Medical Academy Uzbekistan. The reference case of Danish woman was taken from an already published article by Rolf Ankerlund Blauenfeldt and his team.

#### Author contributions

Author Dr. Muhammad Arsalan Ali Sajid and Dr. Hassan Muhammad were involved in solving the case problem, and discussing the case with different professionals, while author Dr. Zayoda Aktamovna and took part in literature review. All authors then reviewed the manuscript collaboratively.

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