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Diclofenac Related Spontaneous Extensive Ecchymosis and Hematoma despite Normal Coagulation Parameters

Ilhami BERBER[1], Mehmet Ali ERKURT[1], Ilknur NIZAM[1,*], Irfan KUKU[1], Emin KAYA[1], Serkan UNLU[2], Mikail YILMAZ[3]

[1]Department of Hematology, Faculty of Medicine, Inonu University, Malatya, Turkey
[2]Department of Radiology, Faculty of Medicine, Inonu University, Malatya, Turkey
[3]Department of Dermatology, Faculty of Medicine, Inonu University, Malatya, Turkey
*Corresponding author: ilknizam@yahoo.com

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Abstract Diclofenac is a member of nonsteroidal anti-inflammatory drugs. In Turkey, ıt is often used as a analgesic. Diclofenac may very occasionally lead to spontaneous extensive ecchymosis and hematoma despite a normal coagulation parameters. In this paper, we report one patient who presented with spontaneous extensive ecchymosis and was diagnosed with a hematoma in the anterior chest wall associated with diclofenac use despite normal coagulation parameters. In countries like Turkey where NSAID are used extensively, drug history should be questioned in patients presenting with spontaneous bleeding and have normal coagulation parameters by physicians.

Keywords: *complication, diclofenac, spontaneous extensive ecchymosis, hematoma*

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1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAID) exert their effect by blocking the enzyme cyclooxygenase that is responsible for prostaglandin synthesis. This enzyme inhibition, in turn, leads to a large reduction in thromboxane synthesis, a condition that resembles a congenital disorder characterized by a tendency to bleed [1]. Diclofenac is a nonnarcotic NSAID with a powerful analgesic action. Its use is associated with a side-effect profile that affects many systems. From a hematological point of view, diclofenac may very occasionally lead to thrombocytopenia, thrombocyte dysfunction, leukopenia, hemolytic anemia, aplastic anemia, and agranulocytosis [2].

Purpura is the local change in skin color caused by extravasated erythrocytes. Purpura is also called petechiae when it is of pin-point size, or ecchymosis, when the spots are larger. It is called a hematoma when the focus of bleeding is encased by a capsule and hematoma fluctuates upon palpation. In thrombocytopenic patients, ecchymosis forms particularly after trauma. It appears because of thrombocyte dysfunction in people with a normal thrombocyte count [3].

In this paper, we report one patient who presented with spontaneous extensive ecchymosis associated with diclofenac use and was diagnosed with a hematoma in the anterior chest wall despite normal coagulation parameters.

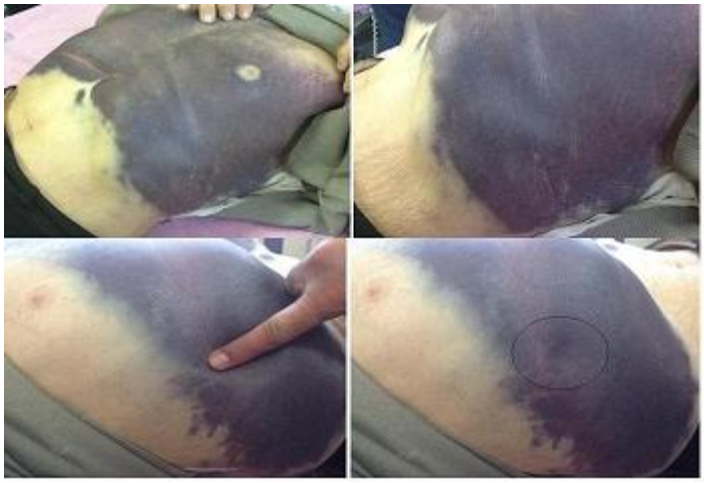

Figure 1a, 1b, 1c, 1d: The images show an extensive ecchymotic lesion at the time of admission; the lesion did not blanch upon pressure

2. Case Presentation

An 85-year-old Turkish man, who was an ex-smoker, presented to our hospital with ecchymosis in the anterior chest wall that had developed within 3 days. He had no history of trauma. His past history was not remarkable, with the exception of chronic obstructive lung disease and osteoarthritis. When specifically questioned about a bleeding diathesis, he gave no history of abnormal bleeding during dental operations or circumcision. There was no family history of any disease. He had been started on oral diclofenac sodium 50 mg twice a day 7 days before at another medical center because of knee pain and he stopped diclofenac 2 days before admitting to our hospital because of stomach ache. His body temperature was 36.5°C, the pulse rate was 96 bpm, blood pressure was 110/70 mmHg and respiratory rate was 14/min. His skin was pale, and there was extensive ecchymosis on the anterior chest wall (Figure 1a, 1b, 1c, and 1d). No abnormally enlarged lymph nodes were palpable in any part of his body. His abdomen was not distended. The spleen and the liver were not palpable. A thoracic computed tomography revealed an appearance consistent with a hematoma the size of 8x5 cm on the left side of the anterior chest wall (Figure 2a, 2b). Laboratory values were shown on Table 1. Diclofenac treatment was stopped, and the patient was monitored for bleeding control. We did not give platelet suspension because of normal platelet count and function. A skin biopsy returned with the result of skin ecchymosis. The patient was discharged without any complications 1 week later.

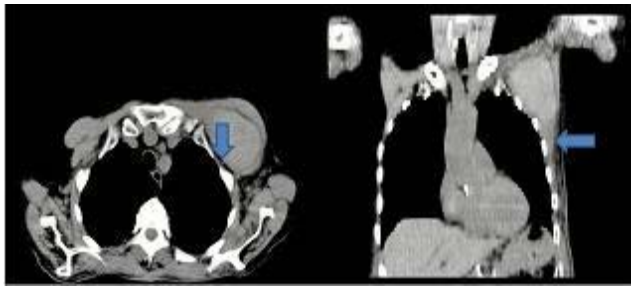

Figure 2a, 2b: An oval-shaped, hyper-dense hematoma between the pectoralis major and minor muscles, as shown by a blue arrow

Table 1. The patient's laboratory values on diagnosis.

Parameter	Laboratory values	Normal Range
Leukocyte count	10.100	4.000-10.000 /microL
Hemoglobin	11.6	13-16 g/dL
Hematocrit	33,5%	39-49%
MCV	88,4	80-95 fL
MCH	30,6	27-33 pg
MPV	7,6	6,8-10,8 fL
RDW	13,4	11,5-14,5%
Platelet count	188.000	150-450x10^3/microL
Prothrombin time	10	9.5-10.5 second
Partial thromboplastin time	27	28-35 sec
Fibrinogen	262	250-400 mg/dL
Bleeding time	9	4-10 minute
Lactate dehydrogenase	220	110-240 U/L
Direct Coombs test	Negative	
Peripheral blood smear	Normal peripheral smear	
Platelet Aggregation Ristocetin (Final concentration of 0,5-0,7 and 1,2-1,5 mg/mL)	89	60%
Platelet Aggregation Collagen (Final concentration of 2-5 µM)	91	60%
Platelet Aggregation ADP (Final concentration of 5-10 µM)	99	60%
Platelet Aggregation ADP (Final concentration of 5-10 µM)	112	60%

3. Discussion

Diclofenac may very occasionally lead to spontaneous extensive ecchymosis and hematoma despite normal coagulation parameters. Personal factors causing the development of ecchymosis and hematoma include trauma, a low thrombocyte count, a coagulation disorder, an abnormally activated partial thromboplastin time, and long-term anticoagulant drug therapy [4].

Stobbe H et al. reported on a study about nonsteroidal anti-rheumatic drugs and hematotoxic lesions. NSAID are the most common medications that interfere with hematopoiesis. Such an adverse effect is important to consider because it frequently leads to an unfavorable prognosis. Immunological reactions should be distinguished from adverse events induced by the toxic effects of drugs, because the former is largely independent of the dosage whereas the latter is not. Aplastic syndromes of the bone marrow are not strictly dose-dependent in every case. The reason may be the particular sensitivity of the hematopoietic stem cells (a stem cell defect) to some drugs [5]. Raineri-Gerber I et al. compared the inhibitory effects of nonsteroidal anti-rheumatic agents diclofenac, acemetacin, mefenamic acid, and ibuprofen on thrombocyte function. They found that the inhibitory effects of acemetacin and ibuprofen were more pronounced than those of diclofenac [1]. Kramer MR et al. reported one case of severe immune hemolytic anemia and thrombocytopenia caused by diclofenac therapy. A 71-year-old woman developed severe immune hemolytic anemia and thrombocytopenia 10 days after the onset of diclofenac therapy. The patient's red blood cells were found to be positive for a warm autoantibody of the IgG type with C3.Stopping the drug

and beginning corticosteroid therapy rapidly improved her clinical status within 3 weeks [6]. Ebstein M et al.reported one case of diclofenac-induced immune thrombocytopenia. Their patient was a scleroderma patient who had developed diclofenac-associated immune thrombocytopenia on two different occasions. Discontinuing diclofenac therapy and beginning prednisone therapy normalized the thrombocyte count [7]. Jick H et al. evaluated the side effects of diclofenac, naproxen, and piroxicam in a total of 100,000 patients. They observed diclofenac-induced hemolytic anemia in only 1 patient [8]. Kim HL et al. reported one case of diclofenac-associated thrombocytopenia and neutropenia. They reported that diclofenac was associated with serious side effects, including thrombocytopenia and neutropenia. They suggested that a complete blood count should be performed and that the drug be stopped immediately when a patient develops symptoms of either thrombocytopenia or neutropenia while on diclofenac therapy [9]. Varoga D et al. reported one case of NSAID-induced, severe platelet dysfunction resulting in a spontaneous compartment syndrome. The authors discontinued diclofenac, which had been regularly used by the patient for 2 years, and operated on the patient for compartment syndrome. They did not use thrombocyte suspension during and after the operation, and successfully discharged the patient with any complication [10]. Hengge UR et al. reported a case who developed purpura fulminans, a manifestation of disseminated intravascular coagulopathy, with rhabdomyolsis following the intramuscular injection of diclofenac [11].

Our patient stopped diclofenac before 48 hours before arriving to hospital. The effect of NSAID on thrombocytes is to reversibly inhibit COX-1, generally to lesser degree than aspirin. NSAID may have caused transient thrombocytopenia, thrombocyte dysfunction via immunological mechanisms and may have also led to endothelial injury via immunological mechanisms. In addition, when immune mechanisms suppressing bone marrow disappear, bone marrow have the potential to produce platelet to maximum $400x10^3$/microL/day [12]. In our patient the most likely explanation is that each of these mechanisms played a role to a certain degree.

4. Conclusion

In countries like Turkey where NSAIDs are used extensively, drug history should be questioned in patients presenting with spontaneous bleeding and have normal coagulation parameters by physicians.

Consent

Written informed consent was obtained from the patient's next of kin for publication of this manuscript and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

This report reflects the opinion of the authors and does not represent the official position of any institution or sponsor. IB was responsible for reviewing previous research, journal hand searching, and drafting the report. MAE, IK, EK, MY and SU were responsible for provision of published trial bibliographies, and preparing photographs. MAE, IN contributed to the final draft of the manuscript and analysis of relevant data. IB were responsible for project coordination. All authors read and approved the final manuscript.

Ethical Approval

This case report was approved by the Institutional Ethics Committee of the Inonu University Medical School.

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