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ORIGINAL ARTICLE

Congenital Alpha-2 Antiplasmin Deficiency: a Literature Survey and Analysis of 123 Cases

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SUMMARY

Background: **Congenital alpha-2 antiplasmin deficiency is a rare, often misdiagnosed coagulopathy that may result in severe hemorrhage. Homozygous patients develop symptomatology in early childhood, while heterozygous individuals may be asymptomatic or bleed profusely following invasive dental procedures, surgery or trauma late in life. Due to the rarity of this entity, we performed an analysis of reported cases of congenital alpha-2 antiplasmin deficiency to share uncommon cases with the medical community, to raise awareness of the condition among clinicians, and to promote better patient management.**

Methods: **To identify relevant studies, PubMed and Science Direct were searched using controlled vocabulary and keywords based on medical subject headings (MeSH). Data of all reported cases of congenital alpha-2 antiplasmin deficiency were extracted and summarized for study setting, patient characteristics, and types of treatments.**

Results: **Thirty-three publications were identified encompassing one hundred twenty-three patients. This manuscript presents many important clinical conditions that are uncommon and may go undetected by medical personnel. It illustrates the importance of considering alpha-2 antiplasmin deficiency in the work-up of patients who present with a severe bleeding phenotype and may have normal coagulation screening tests. Management of such patients may be challenging especially when the diagnosis of alpha-2 antiplasmin deficiency is not known.**

Conclusions: **Improved awareness and access to diagnostic tools will contribute to better management of rare coagulopathies.**

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INTRODUCTION

Alpha-2 antiplasmin (A2-AP) is the major physiological inhibitor of plasmin. It plays a role in the regulation of intravascular fibrinolysis [1]. Decreased levels of A2-AP will lead to increased capacity of the fibrinolytic function and subsequent bleeding symptoms due to insufficient or no inhibition of plasmin [2]. Congenital alpha-2 antiplasmin deficiency is an extremely rare autosomal recessive disease; the real prevalence is not known [3,4].

In Morocco, there is no national registry reporting cases of coagulopathies, especially A2-AP deficiency. To

date, to the best of our knowledge, there has been a report of two cases of congenital A2-AP deficiency from Morocco [5].

Bleeding tendency in homozygous deficiency is often severe and appears in early childhood. Although, some patients present only moderate bleeding.

The majority of heterozygous subjects are asymptomatic. However, some of them may bleed profusely later in life after trauma, dental extraction, and surgery [6]. This coagulopathy is often misdiagnosed, since it presents with normal screening tests for platelet function, bleeding time, Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), and clotting [7]. It is a rare but serious disorder that may lead to fatal hemorrhage. Since there is limited information on its manifestations and response to therapy that could be used as guidelines, management of such patients may be challenging especially when the diagnosis of A2-AP deficiency is not known [3-8]. The diagnosis should be excluded by specific functional and immunological tests for A2-AP, in all patients with an unknown bleeding disorders [6].

In the present paper, we review the published cases of congenital A2-AP deficiency, our understanding of its physiopathology, clinical manifestations, investigations, and our current knowledge of its management.

MATERIALS AND METHODS

Source material was selected from citations listed in Pub Med and Science Direct, as well as the references cited in the selected papers. Searches were limited to studies published from 1986 (the year of the first reported case) to December 2019 (the date of the systematic review). Key search words included: "alpha-2 antiplasmin", "deficiency", "congenital". We did not impose any restrictions while searching. For each study we collected the available data of clinical information including patient origin, age, gender, manifestations and severity of bleeding, type of plasmin inhibitor deficiency and treatment options.

RESULTS

Thirty-three publications were included in this analysis, reporting the existence of presumably 123 cases of homozygous or heterozygous deficiency of alpha-2 antiplasmin including those mentioned in reports as a similar case in the family. The first case of alpha 2-antiplasmin deficiency was reported by Masateru Kohakura in a 16-year-old boy with a condition of repeated bleeding in 1969 in Japan, which was confirmed later in 1978 [9]. A recent condition was described in 2019 in USA by Nakazawa Maria in a 67-year-old male with known history of homozygous alpha-2-AP deficiency. The patient had one sister with homozygous A2-AP deficiency and two heterozygous sons. He was diagnosed at the age of 33 after repeated spontaneous and severe post traumatic bleeding episodes, previous intracranial hemorrhage in 2013, and a prior right humeral fracture requiring surgical intervention, displaced distal left femur fracture status post trauma, all well controlled with antifibrinolytic therapy and fresh frozen plasma (FFP) infusion [3]. To date, there has been one report of two cases of A2-AP deficiency from Morocco [5]. A third case has been confirmed in a 50-year-old male Mr. K. S, who was admitted to intensive care unit of Ibn Rochd University Hospital in Casablanca, Morocco, for severe hematemesis and hemothorax after a traffic accident. At birth the patient did not show any abnormal umbilical bleeding but at the age of 2, he bled for several days after circumcision. Beside this episode the patient did not experienced any hemorrhagic complications. At the age of 45 years old he was diagnosed with a gastro intestinal ulcer. The family history revealed the death of his brother due a major hemorrhage after tooth extraction. Unfortunately, these personal and family histories of bleeding have never been investigated.

Routine coagulation screenings were normal on admission and the results of screening tests gave no indication of impaired primary hemostasis and coagulation. Besides the intensive fluid resuscitation, our patient received two units of red blood cells and five units of fresh frozen plasma (FFP) and was treated with tranexamic acid (Exacyl 1 g/8 h), proton pump inhibitors (40 mg/12 h). After fluid infusion and blood transfusion, a bedside thoracentesis was performed. Four liters of bloody fluid was drained over the first 48 hours.

Esophagogastroduodenoendoscopy (EGD) was also performed, showing a massive diffuse bleeding. It was complicated with a profuse gastrointestinal bleeding causing hemodynamic instability and consciousness deterioration requiring endotracheal intubation, noradrenalin 2 ml/h, 6.0 mg of recombinant factor VIIa, tranexamic acid 1 g/8 h, 3 units of red blood cells, 6 units of FFP, and 8 units of platelets. After he had been stabilized, exploratory laparotomy was performed showing a massive bleeding without any individualized lesion. Despite the attempt to control bleeding, the patient went into circulatory collapse then cardiac arrest.

Treatment with red blood cells, platelets, FFP, anti-fibrinolytic agents and a bolus of FVIIa was ineffective and the patient died on the fifth day of hospitalization. Specific tests for plasminogen, A2-AP, and other physiological inhibitors (α2-macroglobulin and α1-antitrypsin) are not available in our country.

On the third day of hospitalization, a venous blood sample of the patient was collected and sent to a specialist coagulation laboratory abroad.

Five days after the patient's death, we received results showing a low level of A2-AP: 29 IU/L (normal value 80-120 IU/L) [10].

Other reports described perioperative and postoperative management in patients with A2-AP deficiency. In the report of Morimoto et al., three sisters had demonstrated mild umbilical bleeding at birth, with a post traumatic

Table 1. Clinical, biological abnormalities and therapeutic data of previous reported cases [6,20,24] (part 1).

	Homozygous												
	Country	**No. of cases**	**Consan -guinity**	**Gender**	**Age (yrs)**	**Bleeding symptoms**	**Type of defi-ciency**	**A2AP activity (%)**	**A2AP Ag (%)**	**Severity of bleeding**	**Treatment**
Koie et al. (1978) [9]	**Japan**	**1**	**yes**	**M**	**25**	**spontaneous and post trauma**	**I**	**< 1**	**< 1**	**severe**	**no data**
Kluft et al. Lancet (1979) [17]	**Netherlands**	**1**	**no**	**M**	**17**	**spontaneous bleeding in joints, muscle, CNS**	**I**	**2**	**< 1**	**severe**	
Miles et al. Blood (1982) [13]	**USA**	**2**	**yes**	**F/M**	**35/-**	**post traumatic**	**I**	**10 - 12**	**< 1**	**severe**	**FFP infusion**
Yoshioka A et al. (1982) [18]	**Japan**	**3**	**no**	**F**	**3M, 2 and 5**	**umbilical bleeding, epistaxis, subcutaneous hematoma, intramedullary hematoma**	**I**	**< 1**	**< 1,5**	**severe**	**tranexamic acid, FFP infusion**
Kettle and Mayne (1985) [14]	**UK**	**1**	**yes**		**33**	**spontaneous post-traumatic and postsurgical bleeding**	**I**	**15**	**< 1**	**moderate**	**tranexamic acid**
Kluft et al. (1987) [19]	**Netherlands**	**2**	**no**	**M/F**	**15/5**	**bleeding after trauma and surgery**	**II**	**4 - 2**	**83 - 92**	**moderate**	**-**
Griffin et al. 1993 [7-20]	**-**	**1**	**-**	**M**	**-**	**post trauma**	**I**	**41 - 53**	**7**	**severe**	**-**
Guermazi et al. (1997) [21]	**Tunisia**	**1**	**no data**	**M**	**33**	**muscular hematoma, hematuria**	**I**	**14**	**< 5**	**moderate**	**tranexamic acid**
Paqueron X (1997) [12]	**France**	**1**	**yes**	**M**	**6**	**severe bleeding after an elective adenoidectomy**	**I**	**24**	**< 1**	**severe**	**surgical hemostasis, tranexamic acid, blood transfusion**
Zarnovicanova M (2000) [22]	**Slovakia**	**1**	**yes**	**F**	**45**	**spontaneous, post traumatic and post-surgery**	**I**	**10**	**2**	**severe**	**tranexamic acid**
Hayward CPM et al. (2005) [23]	**Canada**	**1**	**no data**	**M**	**50**	**delayed bleeding after surgeries and dental extraction. spontaneous bleeding into his kidney, spleen**	**ND**	**no data**	**NR**	**severe**	**tranexamic acid and FFP**

Table 1. Clinical, biological abnormalities and therapeutic data of previous reported cases [6,20,24] (continued part 2).

	Country	No. of cases	Consan -guinity	Gender	Age (yrs)	Bleeding symptoms	Type of defi-ciency	A2AP activity (%)	A2AP Ag (%)	Severity of bleeding	Treatment
Maino A et al. (2008) [24]	**Kuwait**	**1**	**yes**	**F**	**29**	**easy bruising, epistaxis and bleeding after injuries and tooth extraction, severe postpartum hemorrhage**	**I**	**< 6**	**< 0.01**	**severe**	**FFP, red blood cells and platelet concen**
Akay M (2019) [25]	**UK**	**2**	**yes**	**F/M**	**18/-**	**easy bruising and bone pain**	**-**	**8 µl/dL 15.3 µl/dL**	**-**	**severe/ mild**	**tranexamic acid and FFP**
Peyvandi et al. Haemophilia 2008; 14:166 - 169 (2008) [20]	**-**	**1**	**-**	**-**	**-**	**spontaneous**	**I**	**< 6**	**< 1**	**severe**	**-**
Vigano S (2018) [35]	**Italy**	**1**	**no**	**M**	**62**	**bleeding after surgery epistaxis**	**I**	**< 1**	**< 0.1**	**severe**	**-**
Nakazawa M (2019) [3]	**USA**	**2**	**no data**	**M/F**	**67/-**	**spontaneous and provoked bleeding episodes**	**no data**	**no data**	**no data**	**severe**	**tranexamic acid , FFP transfusion**
Prabhudesai1 A et al. (2019) [2]	**India**	**2**	**yes**	**M/F**	**59/ 28**	**spontaneous and provoked bleeding/ menorrhagia**	**I**	**28/26**	**< 5/< 5**	**severe**	**tranexamic acid, FFP transfusion oral contraceptive**
						Heterozygous					
Aoki et al. (1979) [6]	**Japan**	**9**	**yes**	**5M/4F**	**-**	**No**	**I**	**39 - 55**	**41 - 59**	**-**	**-**
Kluft et al. (1982) [26]	**Netherlands**	**16**	**no**	**-**	**-**	**6/16**	**I**	**47 - 71**	**32 - 64**	**mild**	**tranexamic acid**
Miles et al. (1982) [13]	**USA**	**5**	**yes**	**3M/2F**	**-**	**2/5**	**I**	**42 - 57**	**31 - 47**	**mild**	**no data**
Yoshioka et al. (1982) [18]	Japan	2	no	M/F	-	No	I	45 - 69	35 - 55	-	-

Table 1. Clinical, biological abnormalities and therapeutic data of previous reported cases [6,20,24] (continued part 3).

	Country	No. of cases	Consan -guinity	Gender	Age (yrs)	Bleeding symptoms	Type of defi-ciency	A2AP activity (%)	A2AP Ag (%)	Severity of bleeding	Treatment
Stormorken H et al. (1983) [27]	Norway	1	yes	M	-	no	1	47	41	–	–
Kordich L et al. (1985) [28]	Spanish	2	no data	2M	45/ his son	bleeding after trauma 2/2	I	20 - 40	25 - 40	moderate	tranexamic acid, blood transfusion
Knot et al. Thromb Haemost 1986;55:375 - 8 [20]	-	1	-	-	-	spontaneous	I	55	41	mild	-
Kluft et al. (1987) [19]	Netherlands	8	no	-	-	1/8	II	40 - 60	80 - 120	mild	-
Leebeek et al. (1988) [29]	Dutch	13	-	-	-	2/13	I	51 - 71	60 - 66	mild	-
Shahian DM (1990) [11]	-	1	no data	M	75	bleeding after surgery	-	52	-	moderate	FFP transfusion
Griffin et al. (1993) [7-20]	-	6	-	-	-	5/6	-	41 - 66	-	severe	-
Ikematsu et al. (1996) [8]	Japan	3	no data	M	79/-	severe subcutaneous hemorrhage 1/3	I	23 - 56	21 - 50	severe	tranexamic acid
Paqueron X (1997) [12]	France	2	yes	M	-	No	I	56 - 58	50 - 60	-	--
Devaussuzenet V.M.P et al. (1998) [15]	France	1	yes	M	6	intramedullary hematoma of the left femoral diaphysis	-	-	-	moderate	evacuation and intramedullary infusion of fibrin glue and antifi-brinolytic

Table 1. Clinical, biological abnormalities and therapeutic data of previous reported cases [6,20,24] (continued part 4).

	Country	No. of cases	Consan -guinity	Gender	Age (yrs)	Bleeding symptoms	Type of defi-ciency	A2AP activity (%)	A2AP Ag (%)	Severity of bleeding	Treatment
Lind et al. (1999) [31]	Denmark	3	no	2M/1F	-	3/3	I	49 - 66	62 - 68	moderate	aprotinin, tranexamic acid, red blood cells transfusion
Zarnovicanova et al. (2000) [22]	Central Slovakia	1	yes	F	-	no	I	51	32	-	-
Hanss et al. Blood Coagul Fibrinolysis 2003; 14:107–111 [20]	-	5	-	-	-	3/5	I	45 - 63	55	moderate	-
Morimoto et al. (2004) [4]	Japan	3	6	3F	3M, 2 and 4	umbilical and provoked bleeding	I	< 10	< 1.5	mild	tranexamic acid
Hayward et al. (2005) [23]	Canada	2	-	2M	50/-	spontaneous and post-surgery	-	62 - 64	-	severe	FFP and fibrinolytic inhibitor therapy
Harish VC et al. (2006) [32]	USA	1	-	M	63	spontaneous bruising	I	35	30	moderate	tranexamic acid
Maino et al. (2008) [24]	Kuwait	1	yes	M	29	no	I	43	41	-	-
Peyvandi et al. Haemophilia 2008; 14:166–169 [20]	-	3	-	-	-	no	I	43	40	-	-
Vijapurkar et al. (2009) [32]	India	1	-	F	-	menorrhagia	-	-	51	moderate	tranexamic acid, FFP transfusion
Dawley B et al. (2011) [34]	USA	2	no	M/F	30	2/2	-	50	-	severe	FFP, aminocaproic acid

Table 1. Clinical, biological abnormalities and therapeutic data of previous reported cases [6,20,24] (continued part 5).

	Country	No. of cases	Consan -guinity	Gen -der	Age (yrs)	Bleeding symptoms	Type of defi-cien-cy	A2AP activi-ty (%)	A2AP Ag (%)	Severity of bleeding	Treatment
Igala M et al. (2013) [5]	Morocco	2	no	2M	73/ his brother	bleeding after surgery	no data	76/82	no data	severe	FFP, red blood cells and platelet concentrates
Vigano et al. (2018) [35]	Italy	1	no	F	15	no	I	62	40	-	-
Nakazawa M et al. (2019) [3]	USA	1	no data	M	67	spontaneous and provoked bleeding episodes	no data	no data	no data	moderate	tranexamic acid, FFP transfusion
Akay M et al. (2019) [25]	UK	2	yes	M/F	-	no	-	low-normal value	-	-	-
Prabhudesai1 A et al. (2019) [2]	India	1	yes	M	26	trauma induced hemarthrosis, bruises and an episode of hematemesis	I	60	28	mild to moderate	-
Aissaoui O et al. (2020) [10]	Morocco	1	no	M	50	delayed bleeding after circumcision, post trauma bleeding	-	29	-	severe	tranexamic acid, FFP, Platelet and red blood cells transfusion, FVII

Data not available (-).

bleeding tendency from childhood on. The sisters required hemostatic management 11 times for intraoral bleeding with 7.5 - 10 mg/kg/6 h of oral tranexamic acid starting 3 hours before procedure and continuing for 7 days later [3,4].

Shahian and Levine reported a case of open-heart aortic valve replacement and coronary bypass in a patient with heterozygous A2-AP deficiency. One day before the procedure, he underwent a plasmapheresis with infusion of 3,000 mL of FFP. The post-operative bleeding was severe but was successfully controlled [3,11]. In a 6-year-old boy, a profound bleeding after an elective adenoidectomy required two surgery attempts to obtain hemostasis. Patient's routine perioperative tests for coagulation parameters were within normal limits. More investigations on fibrinolysis were then performed and revealed homozygous A2-AP deficiency [12].

A notable feature was described in a Dutch and an American family, who have experienced severe bleeding in heterozygous subjects [13]. In contrast, heterozygotes in other families had no or mild to moderate bleeding tendency [14].

Another notable and rare symptom of this entity is intramedullary hematoma in the long bones which has been reported in 6-year-old boy, who presented with a sudden pain in his left leg without any history of trauma. MRI showed homogeneous hyperintense signal in the medulla of the femoral diaphysis on both T1 and T2 signals [15]. This particular bleeding symptom was also described in 3 Japanese sisters, who were successfully operated on by using antifibrinolytic agents [16].

We summarized the clinical and biological findings of homozygous and heterozygous reported cases of A2-AP (Table 1).

DISCUSSION

Fibrinolysis is a multifunctional proteolysis system, leading to dissolution of fibrin clots to maintain blood fluidity. It is also involved in tissue development [18]. Fibrinolysis occurs when the plasminogen protein precursor is converted to the active serine protease plasmin by tissue plasminogen activator (t-PA) [4]. This system is highly controlled by a balance between plasminogen activation, inhibition of this activation, and plasmin activity [13].

Dysregulation of the fibrinolytic process contributes to the occurrence of bleeding or thrombosis. For bleeding, two inhibitor deficiencies have been identified, alpha-2 antiplasmin and plasminogen activator inhibitor 1(PAI-1) [8].

Alpha-2 AP or plasmin inhibitor is the major regulator of fibrinolysis [36]. The gene coding for A2-AP is polymorph and is located on chromosome 17 (17pter-p12), containing 10 exons and nine introns spanning approximately 16 kilobases of DNA [6-8]. The mature human inhibitor is a single chain protein of 464 amino acids with the NH2-terminal Met (Met-form) [37]. This protein is converted to the 452 amino acid with the NH2-terminal Asn (Asn-form), which is more physiologically active than the Met form [38].

It is now known that A2-AP is produced not only in the liver [39,40], but also in the kidney and brain [1,41]. Acquired A2-AP deficiency may occur in patients undergoing thrombolytic therapy, patients having severe liver or renal disease, amyloidosis, and disseminated intravascular coagulation [8,36].

Lack of this inhibitor or its congenital deficiency induces a premature dissolution of hemostatic plugs and leads to hemorrhagic tendencies [6].

Congenital deficiency of A2-AP is a rare autosomal recessive bleeding coagulopathy [24]. Homozygotes in general have a severe bleeding tendency often present during childhood, such as umbilical bleeding [8]. Intramedullary hematoma have been described as unusual and rare localization of bleeding in this condition, causing chronic bones pain [6].

Heterozygotes are typically asymptomatic. Although they may have normal levels of inhibitor [28,36], some of them have experienced significant bleeding late in life in response to trauma, surgery or dental procedures [30,32].

Suspicion of A2-AP deficiency can be confirmed with specific functional and immunological tests. Two types of this disorder were recognized: type I characterized by low levels of both activity and antigen, and type II deficiency with a decrease in A2-AP activity but normal antigen concentration [3]. Biological diagnosis of A2-AP deficiency is usually a diagnosis of elimination and sometimes is difficult to achieve, especially in resource limited countries like Morocco, where the study of coagulopathies may not be a priority. Indeed, since there is no simple coagulation test that raises suspicion of this diagnosis, patients with unknown bleeding are investigated several times to identify an etiology by the usual screening tests that remain normal (Prothrombin Time, activated Partial Thromboplastin Time, fibrinogen, platelet aggregation, and clotting factor titers). The diagnosis of this disorder requires specific measurement of A2-AP which is not always performed [6].

The management of bleeding episodes involves drugs that inhibit fibrinolysis, such as tranexamic acid and aminocaproic acid. The antifibrinolytic agents have effects like A2-AP and inhibit the competitive binding of plasmin to fibrin [42,43]. Tranexamic acid can be used in response to hemorrhagic complication or as prophylaxis before surgical procedures [9]. Fresh frozen plasma (FFP) can be used as an alternative to antifibrinolytic agents [11] and should not be selected as the first treatment option for achieving hemostasis, because the rate of increase in A2-AP activity induced by FFP is low and may vary depending on its method of preparation [4]. The treatments of choice remain antifibrinolytic agents [5]. It has been recommended to administrate an intravenous bolus accompanied by oral administration of tranexamic acid for several days to maintain a sustained anti-fibrinolytic activity [4]. Desmopressin commonly used to manage bleeding, should be avoided in this disorder because it may induce secretion of plasminogen activator [11]. Intramedullary hematomas are typically well managed with surgical evacuation and intramedullary instillation of a combination of tranexamic

acid and fibrin glue [44].

The case of Mr. K. S from Morocco highlights the challenges that clinicians may be faced with while managing patients with severe bleeding manifestations and a normal coagulation profile. Due to the rare occurrence of this coagulopathy and the difficult access to diagnostic tests, the diagnosis in this case unfortunately was performed after the patient's death and, unlike other individuals with A2-AP deficiency, the patient did not respond to current therapy as reported. Thus, it is important that we keep reporting and sharing our cases, experiences, and findings with the medical community to enhance awareness of this disorder among clinicians and to promote patient's management.

Table 1 shows the previous reported cases of plasmin inhibitor deficiency. We noticed a large interval of activity levels in many patients with severe bleeding history due to both presumed homozygous or heterozygous A2-AP deficiency. It is suggested in literature that the importance of bleeding seems to be correlated with the severity of the deficit [13]. One sixth (16/99) of presumed heterozygous subjects has experienced severe bleeding episodes. Variable clinical expression of alpha-2 antiplasmin deficiency may be related to age-related vascular changes and association with other abnormalities [6-30].

In Igala's report, the patient and his brother suffered from moderate to severe bleeding with plasmin inhibitor activity of 76% and 82%, close to the lower limit of the normal range (98 - 122%) [5]. In such cases with plasmin inhibitor activity levels as high as 50%, the evaluation of plasmin inhibitor antigen is essential to not miss the diagnosis of heterozygous plasmin inhibitor deficiency.

Some previous publications have reported poor specificity of commercially available plasmin inhibitor activity reagents, and it has been related to α2 macroglobulin-plasmin complex increased formation at low plasmin inhibitor levels [20,45]. Pozzi concludes in this context that the reduced plasmin concentration in tests is essential to improve specificity [20].

This manuscript presents many important clinical conditions that are uncommon and may be undetected by medical personnel, especially in areas where the study of coagulopathies may not be a priority within the health systems. The occurrence of alpha 2-antiplasmin deficiency in Morocco, therefore, warrants publication as a means to raise awareness of the condition among clinicians and to promote better global patient care in general.

Contribution of Authors:

All the authors contributed to the conduct of this work. All authors also state that they have read and approved the final manuscript.

Declaration of Interest:

The authors declare that there is no conflict of interest regarding the publication of this paper.

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