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# Massive Gingival Hemorrhage after Laser Gingivoplasty Revealing Scott 'S Syndrome

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***Executive Summary**:*
*Hemorrhagic complications in the aftermath of oral interventions are quite frequent and sometimes constitute a serious issue in stomatology. These situations mainly concern patients who are monitored for cardiovascular pathologies and are on anticoagulants. Although, certain general pathologies have a component on hemostasis and consequently entails a risk of bleeding. These cases require appropriate preparations before any surgery. However, dental bleeding that is difficult to control can be triggered by certain therapeutic procedures and thus lead to the diagnosis of pathologies not known hitherto in certain patients.*
*In this study, we shall report a very rare case of a 32-year-old patient who experienced significant bleeding following periodontal laser surgery and was diagnosed with Scott's syndrome based on various hematological investigations.*

***Keywords:*** *Laser gingivoplasty – Oral hemorrhage – Phosphatidylserine – Scott's syndrome – Anoctamin6*

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## I. Introduction

Periodontal care is a common therapeutic procedure in dental surgery and stomatology. Unfortunately, these interventions can be complicated because hemorrhage can occur in certain situations **[1]** The profiles at risk of bleeding are mainly patients on anticoagulant treatments, patients undergoing hemopathies treatment or other general diseases with an impact on hemostasis. However, seemingly healthy patients with no known history of bleeding may present remarkable amount of bleeding on a first dental treatment due to previously undiagnosed hemostasis disorders. **[2]**

We shall report in our paper a rare case of a patient who was diagnosed with Scott's syndrome, because of a secondary hemorrhagic complication caused by a periodontal treatment performed with laser.

Scott's Syndrome is a very rare hemorrhagic disorder that was named after the first patient diagnosed with this condition. It reflects a functional deficiency of the platelet plasma membrane that is incapable of exposing procoagulant phospholipids to its surface. Its exact prevalence is unknown to date and is estimated to be about 1 case per 1,000,000. **[3]**

## II. Observation

A 32-year-old female patient with a history of factor XII deficiency was admitted to our department for the treatment of chronic gingivorrhagia following a laser procedure she had for gingival recession 5 weeks earlier.

The admission evaluation results indicated that the patient was slightly anxious but in good condition. On buccal examination, we note the presence of a large left palatal coagulum with a submucosal detachment extending from the gingival papilla from tooth 22 to tooth 26, with a sheet-like blood flow covering the entire sector II.

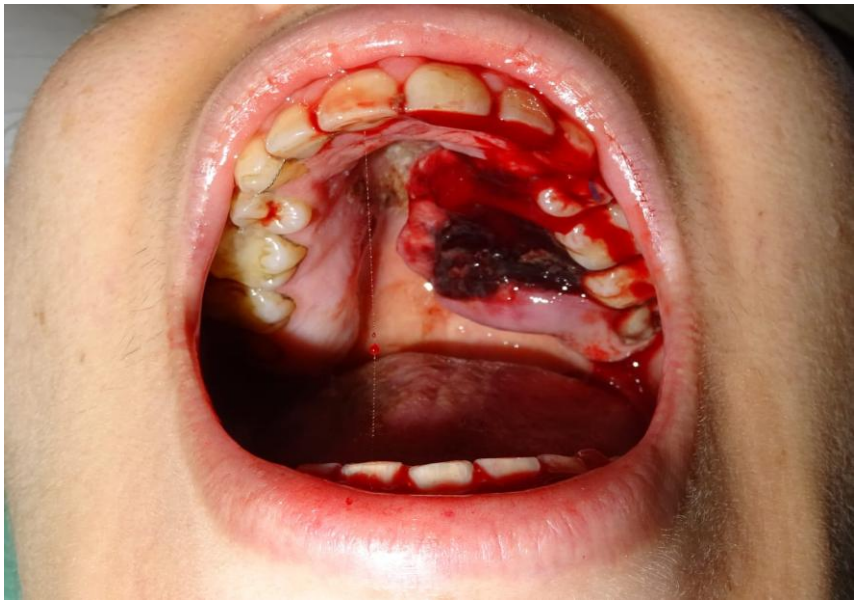

**Figure 1**: Oral cavity upon admission.

A biological assessment was carried out on admission, namely: a blood count, a hemostasis test, and a liver test. No hemostasis disorders or deglobulation were detected.
The maxillofacial CT scan confirmed the presence of a circumscribed mass on the left palate extending towards the premolars and molars which corresponds to a large left palatal hematoma.

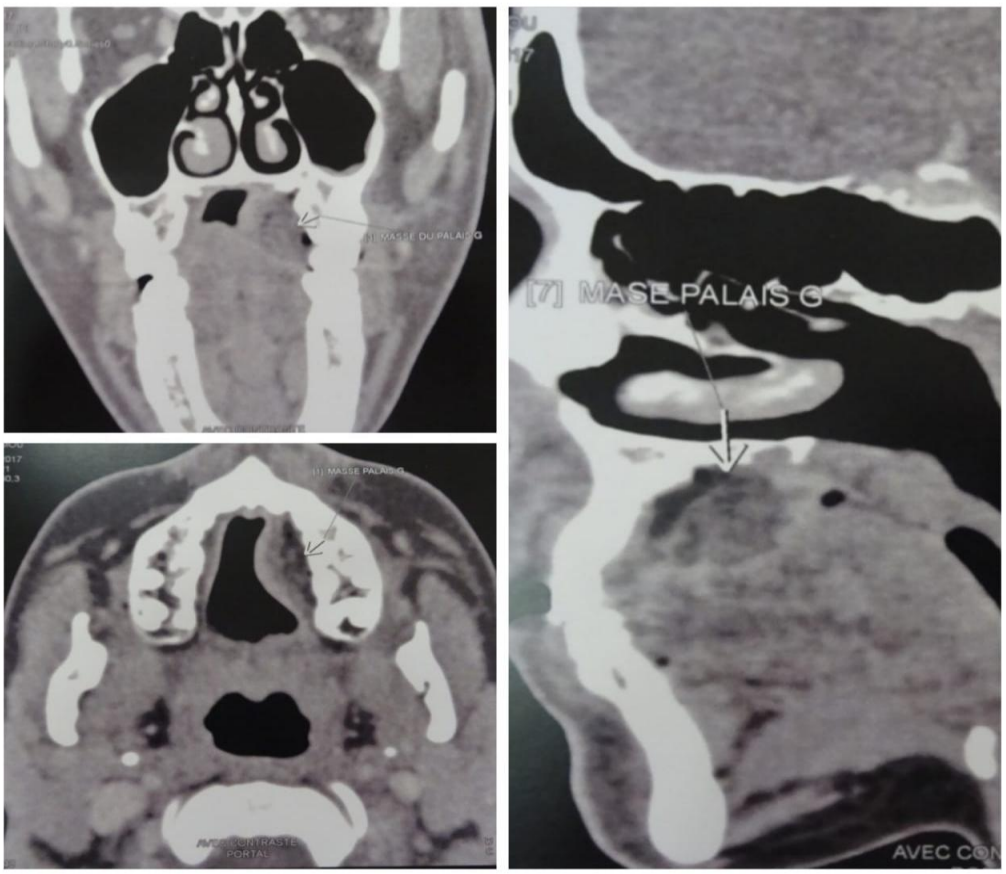


**Figure 2**: Maxillofacial CT in sections (axial, coronal and sagittal) showing the presence of a left palatal mass
Under local anesthesia, we cleaned the oral cavity in the dental chair, from the intra-sulcular sutures to the resorbable thread to bring the gingival mucosa closer and flattened. A compression will then be maintained by a compress soaked in Exacyl®.

The patient was placed on Exacyl® 500, 3 tablets per day and received a transfusion of 4 pellets of fresh frozen plasma. The post-operative phases were marked by persistent bleeding during the first 24 hours of hospitalization, followed by a progressive improvement until the effective formation of a blood clot which was gradually strengthened.

The patient will be discharged after one week when the bleeding has completely ceased.

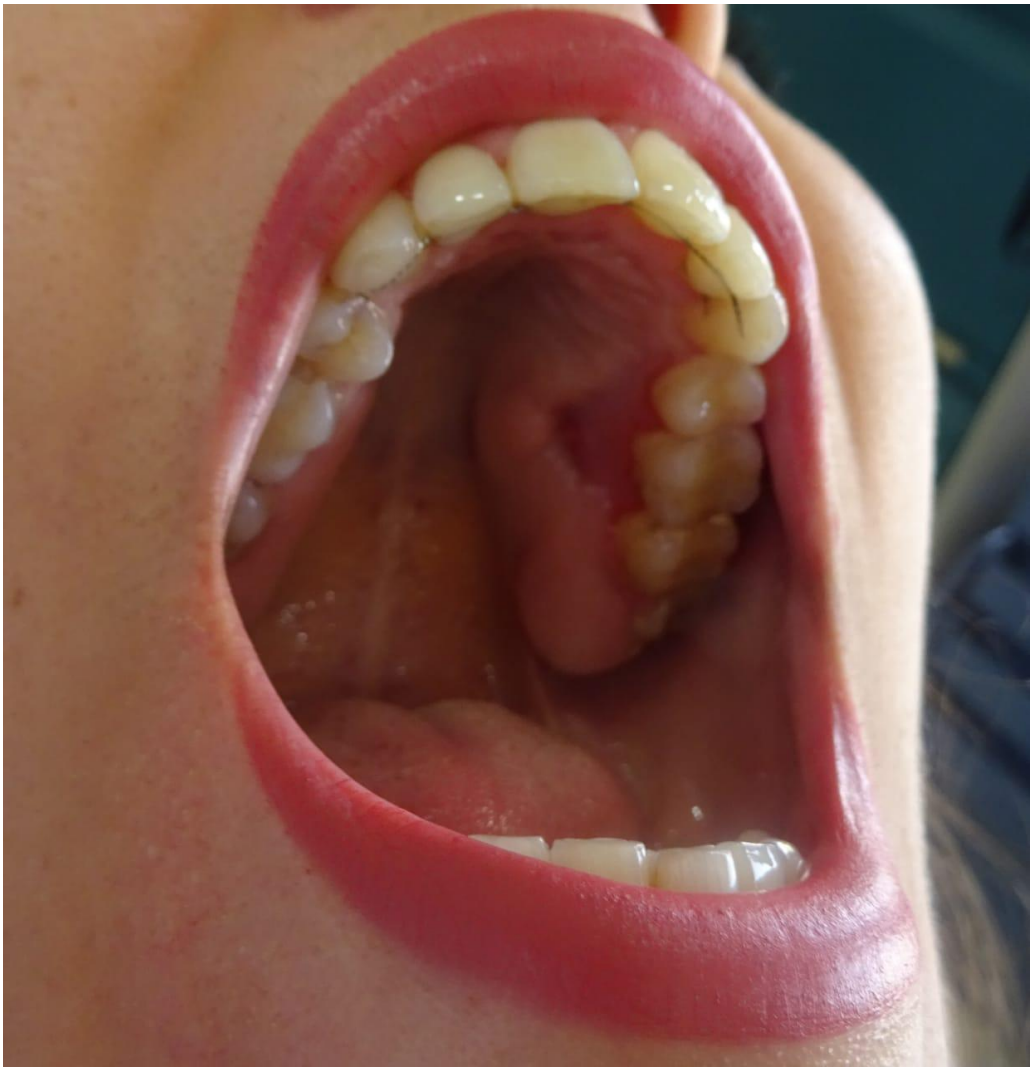

**Figure 3**: oral cavity during a 4-month check-up

Despite the patient's known factor XII deficiency, which is a rare hematological abnormality with no real hemorrhagic impact, a complementary biological evaluation was carried out to explain the origin of this bleeding. Unfortunately, it did not give any tangible explanation.

The new blood count was found to be normal. The functional hemostasis assessment allowed us to observe a decrease in thrombin production. The maximum thrombin concentration time was high at 7.17 minutes (Normal values: 4- 6 minutes) with a decreased velocity at 59.78 nanomol/minutes (Normal values: 67-235 nmol/min). The thromboelastometry objective is an extension of the coagulation time to 190 seconds (Normal values: 110 to 173 s). Platelet functional exploration showed no alteration on aggregation and agglutination induced by ristocetin tests.

Cytometric analysis of platelets reported only 6.7% of positive platelets after activation with 10-4 M calcium ionophore. Thus, we observe a significant defect in the platelet procoagulant phospholipid phrase upon stimulation. These results allowed us to confirm the diagnosis of Scott's syndrome.

The patient was admitted a second time to our hospital for the treatment of a chronic ulcerative lesion of the medial malleolus of the left foot due to a mild trauma. She benefited from a dressing with PRP (platelet rich plasma) biological glue, and the outcome was also successful with complete recovery after 2 weeks.

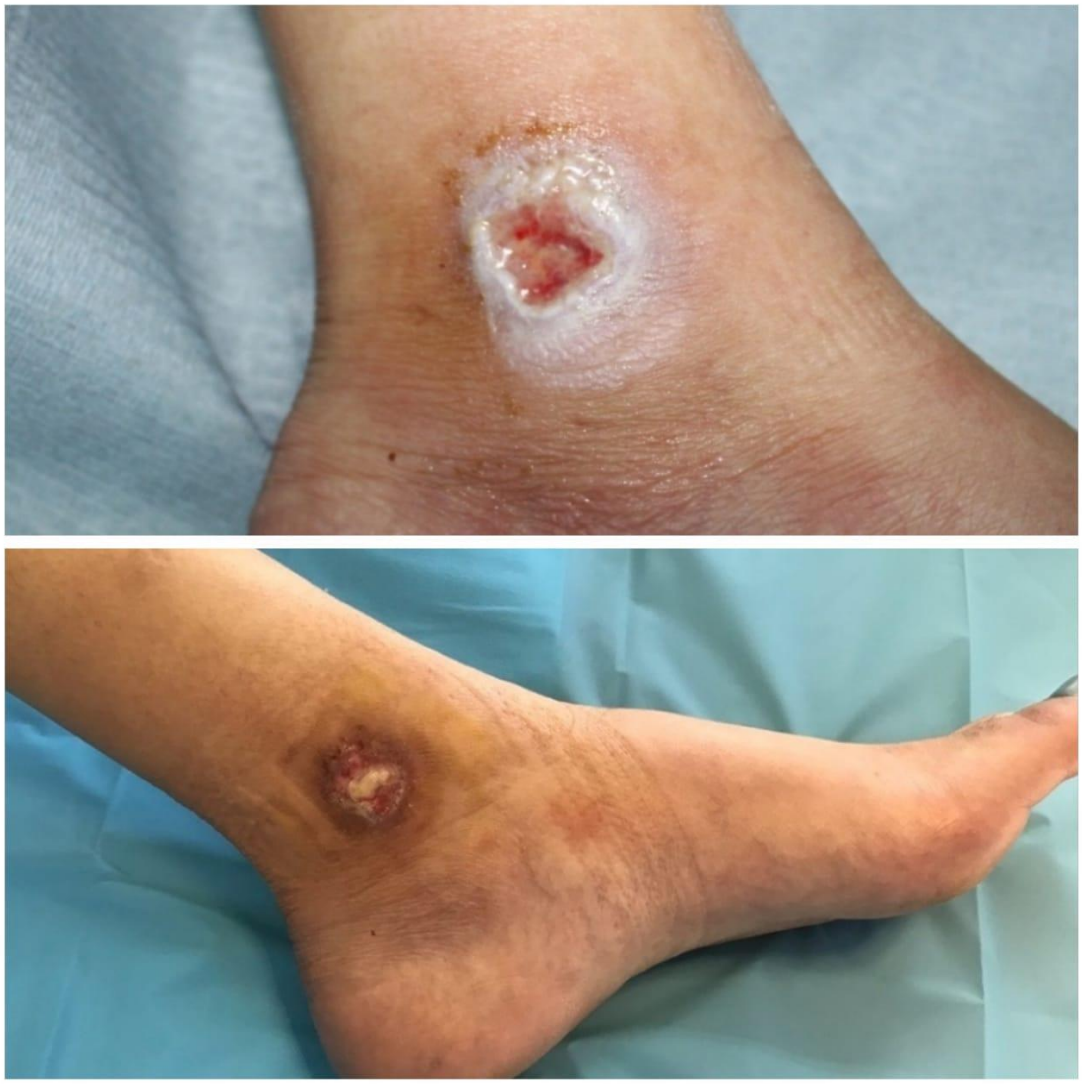

**Figure 4**: Injury of the internal malleolus of the left foot before and after healing

## III. Discussion

Gingival recession is defined as the apical shift of the marginal gum. It results in a loss of gingival attachment, thus exposing the root surface to the buccal tract. Commonly referred to as tooth loss, this situation can be caused by several congenital or inherent factors, related to lifestyle patterns or to certain pathologies. **[1,4]** Although prevention remains the best treatment, depending on the evolution of the pathology, a gingivoplasty or a gingival graft can be proposed. The use of the laser for gingival surgery is a fairly common practice, but hemorrhagic complications can occur in case of abnormal hemostasis as in any dental procedure. We can often control this bleeding by several therapeutic methods.

These hemorrhages, which can sometimes be drastic, are often encountered in patients with antiaggregation or anticoagulant treatments, or in patients with pathologies that present a high risk of bleeding. **[2, 6]**

Hemostasis can be defined as the set of physiological phenomena that allow the prevention and cease of bleeding. It comprises of 3 stages which are primary hemostasis, plasma coagulation and fibrinolysis. It is therefore a well-paced phenomenon which subtly aims at a balance between a coagulating process which may likely lead to a thrombotic accident and a process of fibrinolysis at hemorrhagic risk. [2] Several factors are involved in this mechanism: blood flow, vascular wall, subendothelium, platelets, factors and inhibitors of coagulation as well as fibrinolysis. Thus, several abnormalities can be recorded during various processes of hemostasis and thus lead to pathological complications such as bleeding that is sometimes difficult to control, or conversely vascular thrombosis.

Physiologically, primary hemostasis results in the formation of a platelet wall that closes the breach. Local vascular time is noted, which consists of a reversible reflex constriction due to the combined action of different mediators. This is followed by the platelet phase which makes it possible to obtain, in the seconds

following the vascular injury the adhesion of the platelets to the subendothelium. Also, the secretion of the substances by the platelets and their adhesion to each other.

As soon as the platelets are strongly stimulated by the first traces of thrombin combined with the collagens of the damaged vascular wall, they will undergo a transformation. This will lead to an increase in the cytoplasmic concentration of calcium and naturally to the rupture of the phospholipid distribution asymmetry of the plasma membrane. Thus, negative phospholipids will be exposed to the surface of the platelets, mainly phosphatidylserine. **[8,9]**

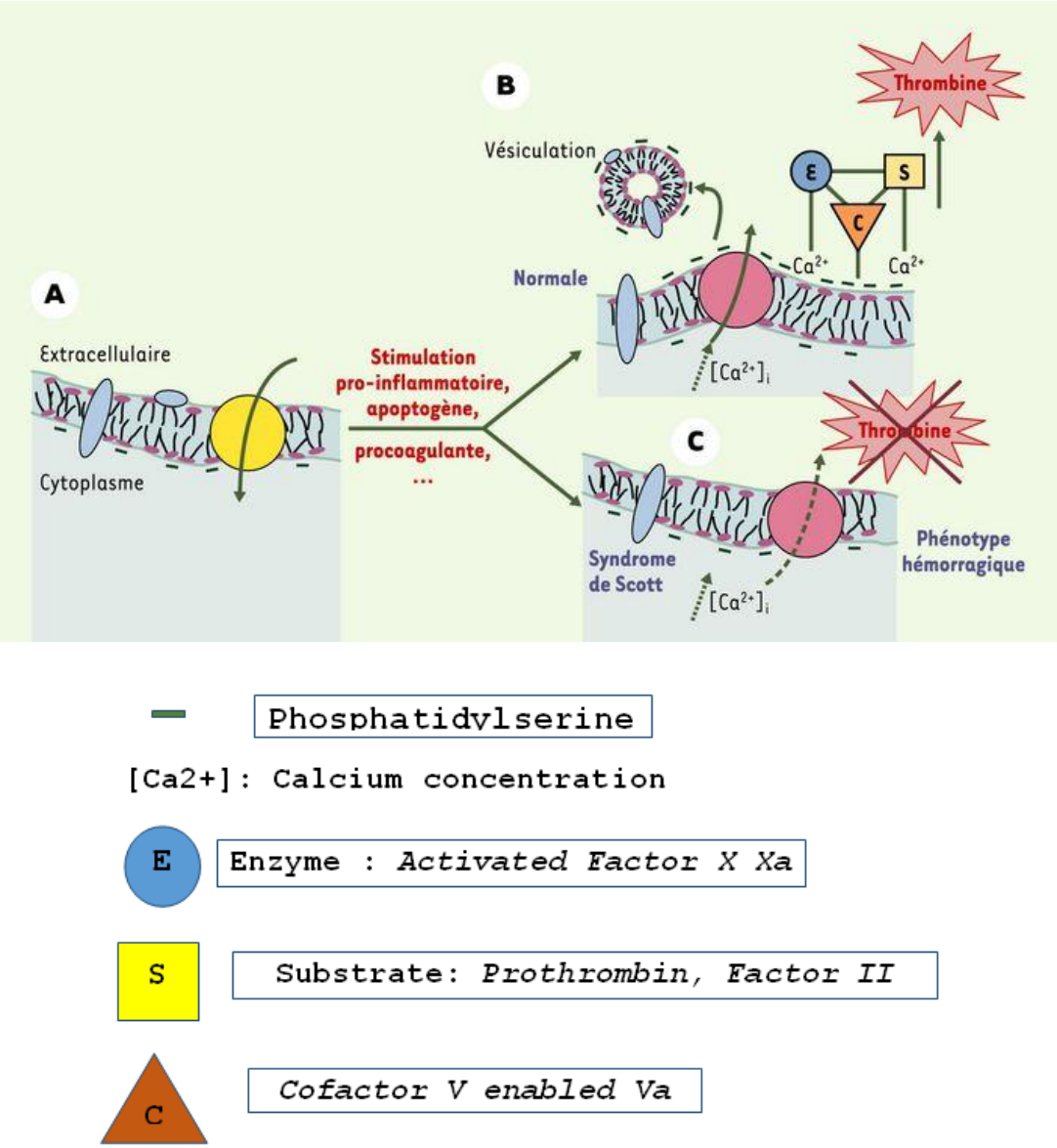


**Figure 5**: Schematic representation of the plasma membrane of the stationary cell (maintenance of membrane asymmetry, **A**), of the stimulated cell (loss of asymmetry, **B**) and lack of outsourcing of phosphatidylserine (Scott's syndrome **C**)

In the illustrative scheme of FIG. 5 above, it is clearly seen that phosphatidylserine (PS) represented by its negative charge (less signs in dark green) is retained in the cytoplasm of the cell at rest under the action of a transporter, called the aminophospholipid translocase (represented in yellow). After pro-coagulant stimulation, there was an increase in the intracellular concentration of calcium, which triggered the transport of this anionic aminophospholipid to the outer layer. As soon as phosphatidylserine is available, the enzymatic complexes of coagulation can be formed. It will be observed that the enzyme (E), which corresponds to activated factor X (Xa), and the substrate (S)corresponding to prothrombin (factor II), which are dependent on vitamin K, interact with phosphatidylserine exposed via calcium ($Ca2^{+}$). The activated cofactor V (Va) illustrated by (C) will attach

to the membrane independently of calcium, but still under the control of phosphatidylserine. From its specific substrate, each complex will produce the following enzyme from the coagulation cascade. The last complex, prothrombinase, shown here can be replicated in vitro to functionally detect the exposure of phosphatidylserine to the cell surface. This enzyme complex formed on the surface of the platelets thus comprises activated factor X (Xa), cofactor Va and phospholipids to which they are bound via calcium. It will ensure the generation of thrombin (activated factor II, IIa) through the proteolytic cleavage of prothrombin (factor II). Indeed, the amount of thrombin produced will be proportional to the degree of expression of phosphatidylserine. In Scott's syndrome, phosphatidylserine is not exposed to the surface of cells undergoing procoagulant stimulation. This results in the lack of formation of coagulation enzyme complexes and the hemorrhagic phenotype in these patients. **[10,11]**

Phosphatidylserine is the main anionic phospholipid useful for the clustering of different activating enzyme sets of the blood coagulation cascade on the surface of stimulated platelets. As its excretion on the surface of the platelet membranes is considerably altered in the pathology of patients with bleeding disorders of various intensity. This functional deficiency will be clearly demonstrated by the determination of residual prothrombin in the serum. **[10]**

Several studies performed on the regulation of phosphatidylserine exposure to the surface of cell membranes have helped us to better understand the pathophysiology of this anomaly. Thus, the presence of several phospholipid transporters at the level of the membrane of the platelets has been evoked.

Scramblase, which is a membrane protein, plays a role in the translocation of phospholipids between the two layers of the lipid bilayer of the cell, but is more involved in hematopoiesis than in the pro-coagulant response.

Flippase and floppase are ATP-dependent enzymes involved in the regulation of membrane asymmetry by ensuring the passage of lipids from the cytoplasm to the extracellular medium and vice versa. Thus, the specific unidirectional movement of phosphatidyleserine would be catalyzed by an ATP and calcium-dependent floppase which would act in the opposite direction to the flippase. Thus, the specific unidirectional movement of phosphatidyleserine would be catalyzed by an ATP and calcium-dependent floppase which would act in the opposite direction to the flippase that maintains it in the cytoplamis. In platelet cells,the ability to transport floppase between the two layers of the plasma membrane would be 20 times greater than the floppase activity of red blood cells. This suggests its direct participation in the hemostatic activity. **[12,13]**

In non-active Scott cells, flippase activity is well functioning. After stimulation, there is a lack of rapid activation of floppase and scramblase, which consequently inhibits the excretion of membrane phospholipids and therefore the hemorrhagic phenotype observed

The important role of calcium has also been emphasized in the theories that trigger this anomaly.

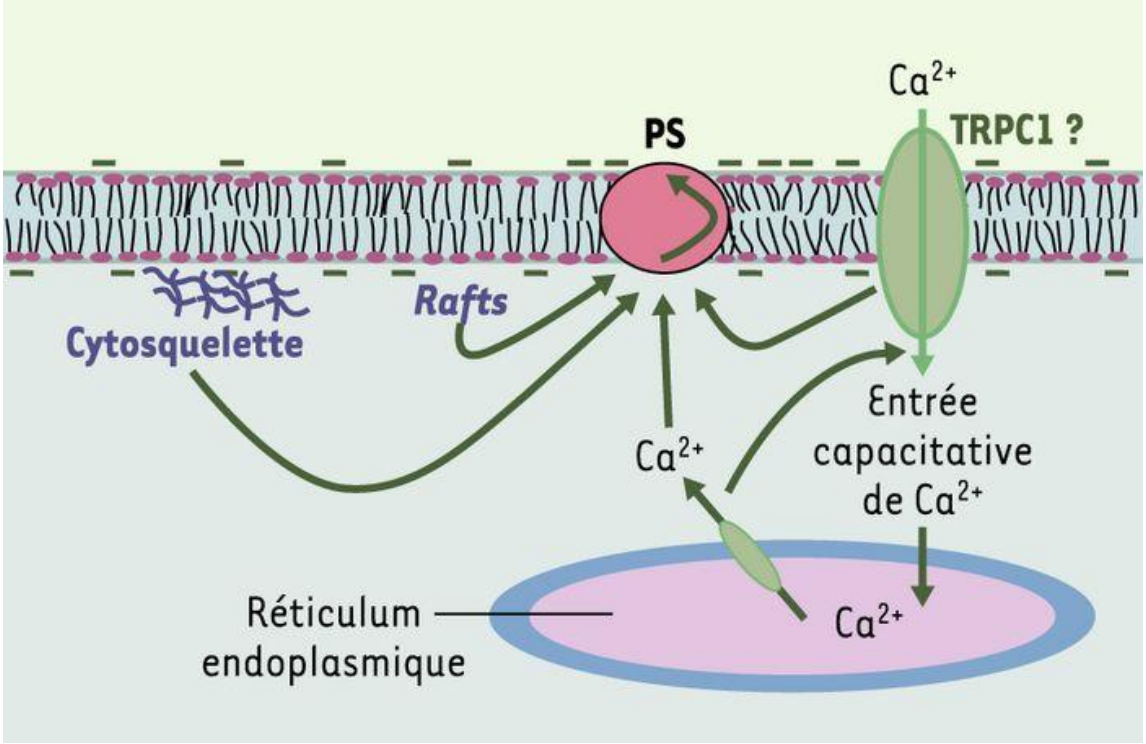


**Figure 6**: Role of calcium in regulating the externalization phosphatidylserine membrane

It should be noted that insufficient Ca2+ entry through the plasma membrane observed in Scott patients would result in the lack of exposure of phosphatidylserine. This failure is thought to be due to a small increase in calcium concentration after cell stimulation. Although, scramblase activity is well functional. **[14]**

The illustrative diagram of FIG. 6 shows the outflow of calcium from the intracellular medium to the membrane of the platelets. This is essential for the externalization of the phophatidylserine which is in principle compensated by a capacitive input of this same element. This will ensure the stock of endoplasmic reticulum and maintain its cytoplasmic concentration high during the time of pro-coagulant stimulation. In Scott patients, this calcium return is almost impossible. **[9]**

The first genetic studies carried out on mice made it possible to conclude the presence of an ABC transporter (ATP-binding cassette), called ABCA1, which would participate in the exposure of phosphatidylserine and the influx of cholesterol. Thus, this study concludes that the profiles that have an ABCA -/- phenotype exhibit the characteristics of the Scott patient in whom we find bleeding disorders associated with phosphatidylserine exposure deficit. The discovery of the first familial case of the pathology led to the hypothesis that Scott's syndrome is transmitted as an autosomal recessive trait reflecting the deletion or mutation of a putative phosphatidylserine translocase to the outside. **[15, 16]**

The role of phosphatidylinositol-4,5-bisphosphate (PIP2) in the imbalance of membrane asymmetry has been reported in some studies. There would be an interaction of the PIP2-Ca2+ complex which would lead to the formation of membrane microdomains, and thus leads to a destabilization of the lipid bilayer allowing a phosphatidylserine PS/ phosphatidylcholine PC exchange.PIP2 plays a regulatory role in Ca2+ -induced scrambling because agents that allow the formation of PIP2 domains cause redistribution of membrane phospholipids. **[17]**

More recently, it has been discovered that anoctamin 6 (ANO6) is a gene which codes for a multidomain transmembrane protein (TMEM16F/Ano6), belonging to the anoctamine family and acts as a scramblase of membrane phospholipids. This protein is an essential component for phosphatidylserine-dependent calcium exposure on the surface of stimulated platelet cells. Significant mutations in this gene, particularly in two essential components, have been found in Scott's syndrome. This situation significantly disrupts the membrane exposure of phosphatidylserine. It should also be noted that apart from scott syndrome, anoctamin 6 (ANO6) is also involved as a gene encoding proteins found in testicular ganadoblastoma. **[18,19,20]**

The diagnosis of Scott syndrome is made by functional prothrombinase dosage and flow cytometry at the platelet level. It should be noted that there is a considerable decrease or absence of thrombin generation and in similar proportions, a defect in phosphatidylserine release.

With regards to treatement, in Scott's syndrome as in most hemorrhagic disorders related to impaired platelet function, systematic treatment is not recommended except when surgery is planned or in the event of injury. Surgeons and dentists should therefore be informed of the patient's condition, in order to plan any medical procedure. For example, Desmopressin (DDAVP® and Octostim®) can be prescribed to reduce blood loss because of its ability to shorten bleeding time. It is also important to mention the usefulness of hormonal treatment used by women, with the aim of reducing the duration and quantity of bleeding during menstruation. Transfusions of platelet concentrates will be performed when the response to Desmopressin is unfavorable, in case of active hemorrhage and before any surgery. **[21,22]**

## IV. Conclusion

Scott's syndrome is an extremely rare congenital abnormality that causes bleeding disorders due to dysfunction of normal phosphatidylserine exposure in the membrane of activated platelets. This abnormality is due to the mutation of the anoctamin 6 (ANO6) gene which codes for the transmembrane TMEM16F/Ano6 protein mainly involved in the membrane exposure of phosphatidylserine in stimulated platelets.

It is necessary to diagnose this pathology, carry out genetic counseling to inform the patient and their family on how to prevent and anticipate any hemorrhagic situation that could lead to a severe outcome.

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