Primary Thrombophilia XIV: Worldwide Identification of Sticky Platelet Syndrome

María Fernanda Vallejo-Villalobos, PhD1  Gisela Berenice Gomez-Cruz, MD2,3
Yahveth Cantero-Fortiz, MD2,4  Juan Carlos Olivares-Gazca, MD2,5  Mauricio Olivares-Gazca, MD2,5
Iván Murrieta-Alvarez, MD2,3  Virginia Reyes-Nuñez, PhD5,6
Guillermo J. Ruiz-Argüelles, MD, FRCP (Glasg), MACP, DSc (hon)2,5

1 Hospital Christus Muguerza Betania de Puebla, Puebla, México
2 Centro de Hematología y Medicina Interna de Puebla, Puebla, México
3 School of Medicine, Benemérita Universidad Autónoma de Puebla, Puebla, México
4 School of Medicine, Universidad de las Américas Puebla, Puebla, México
5 School of Medicine, Universidad Popular Autónoma del Estado de Puebla, Puebla, México
6 Laboratorios Clínicos de Puebla, Puebla, México

Address for correspondence Guillermo J. Ruiz-Argüelles, MD, FRCP (Glasg), MACP, Dsc (hon), Centro de Hematología y Medicina Interna de Puebla, 8B Sur 3710, 72530 Puebla, Mexico (e-mail: gruiz1@clinicaruiz.com).


Sticky platelet syndrome (SPS) is a prothrombotic platelet disorder characterized by increased in vitro platelet aggregation after activation with low concentrations of adenosine diphosphate and/or epinephrine.3–67 Recently, Favaloro and Lippi68 provided a commentary on the increasing number of papers published on SPS along the historical timeline, since its initial description in 1988,3 and in response an update review was also published in this journal.67 As noted in both reports,66,67 the condition is not recognized by all workers involved in the study for treatment of thrombophilic conditions. One reason to explain the fact that some researchers recognize SPS as a genuine thrombophilic condition whilst other do not is that not everybody employs the same criteria to define the condition. We and others,11,53 attempting to standardize its investigation, employ the criteria originally described by Mammen et al3 to define SPS, and accordingly, our group has been able to show that around 15% of Mexican mestizo persons within the general normal population meet the criteria to identify them as bearers of SPS and that this figure goes up to 60% in Mexican mestizo patients with a clinical marker of inherited thrombophilia. Accordingly, we have been able to gather prospectively a group of 165 Mexican mestizo patients with SPS, 121 of whom (66.7%) display another thrombophilic condition in addition to SPS. Employing the database PubMed, we similarly looked for all entries using the term “sticky platelet,” either in the title and/or in the body of the abstract. The salient features of each publication were then further analyzed. The initial search identified a total of 108 papers. Forty-one of them included the combination of words but did not actually describe SPS and were accordingly discarded; 24 papers comprised reviews about SPS and 43 papers described either cases or series of patients; these latter 43 papers were further analyzed. The first paper describing patients with SPS was identified to be published in 1988, and was authored by Mammen et al.3 Since then and until February 2019, as noted above, 67 papers were identified.1–67 ►Fig. 1 depicts the number of papers published as a cumulative timeline, whereas ►Fig. 2 depicts the countries in which these papers were published. It is interesting to note that the country with the largest number of papers published on SPS is the United States with a total of 14, followed by Slovakia with 12, Germany with 8, and México with 6, whereas Hungary, Turkey, Russia, and New Zealand had only 1 publication each. What is also interesting is the absence of reports from most other geographies (►Fig. 2).

A total of 1,783 patients with SPS have been described and published in these 30 years (1988–2019) of reports. The rate of description of these cases has increased in the last 10 years (►Fig. 1). The most number of cases have been identified and published in Slovakia (n = 451), followed by the United States (n = 451), México (n = 322), Germany (n = 88), and Russia (n = 70). The thromboses identified in these patients were both venous and arterial; in some patients SPS was identified together with another thrombophilic condition, either inherited or acquired. ►Table 1 gathers the salient information from all these publications. Most patients (72%) were treated with aspirin and/or other antiplatelet drugs, whereas 27% were given oral anticoagulants or heparin.

According to several publications, SPS is thought, at least by several investigators, to be the most common inherited
prothrombotic platelet defect and thus likely to be of the greatest clinical importance. The recognition of SPS as a genuine entity has prompted the development of both promoters and opponents to the concept. Up to now, the lack of a definite molecular basis for the condition has been a major obstacle for its acceptance by many as a distinct entity and several skeptical scientists remain reluctant to consider this disease as a true distinct clinicopathological entity. On the other hand, unlike plasma-based hemostasis research work, the study of SPS requires fresh patient material and highly meticulous sample collection and handling; as a consequence, the patients under investigation require blood collection at the time of investigation, and then platelet function testing needs to be performed immediately afterwards by experienced personnel. Some hemostasis experts still consider the aberrant platelet aggregation responses seen in this condition as laboratory artifacts; however, SPS seems to be building up an increasing belief base, if we accept that the increasing publication rate on the topic (66; Fig. 1), coupled with the additional information presented here, represents increasing acceptance of SPS as a prothrombotic condition. Taking into account the number of inhabitants in each of the countries which have reported cases of the SPS, it is clear that the countries which have made the most contributions on SPS per number of inhabitants are Slovakia and México; this finding reflects mainly the interest in the condition of groups of scientists living in these two countries, headed by

Fig. 1 Cumulative frequency distribution curve along time of papers published on the sticky platelet syndrome between 1988 and 2018 inclusive.

Fig. 2 Countries in which the sticky platelet syndrome has been described between 1988 and 2018 inclusive.
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Year</th>
<th>Cases</th>
<th>Location of thrombosis</th>
<th>Treatment</th>
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</thead>
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<tr>
<td>Mammen et al</td>
<td>United States</td>
<td>1988</td>
<td>7</td>
<td>MI</td>
<td>Aspirin</td>
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<td>Berg-Dammer et al</td>
<td>Germany</td>
<td>1997</td>
<td>2</td>
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<td>Heparin/aspirin/catheter/thrombolysis</td>
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<td>Baker and Bick</td>
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<td>1999</td>
<td>153</td>
<td>DVT/stroke/MI/retinal vein</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Chaturvedi and Dzieczkowski</td>
<td>United States</td>
<td>1999</td>
<td>1</td>
<td>Acute stroke</td>
<td>Heparin/warfarin</td>
</tr>
<tr>
<td>Bick</td>
<td>United States</td>
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<td>21</td>
<td>Recurrent miscarriage</td>
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<td>Weber et al</td>
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<td>DVT/retinal vein thrombosis/portal vein thrombosis/pulmonary embolism</td>
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<td>Frenkel and Mammen</td>
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<td>Lewerenz et al</td>
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<td>Kubisz et al</td>
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<td>Fodor et al</td>
<td>Hungary</td>
<td>2007</td>
<td>1</td>
<td>Left internal carotid artery</td>
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<td>Mühlfeld et al</td>
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<td>Renal allograft rejection/colonic microinfections/ pulmonary embolism/DVT</td>
<td>Heparin/aspirin</td>
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<tr>
<td>Randhawa and Van Stavern</td>
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<td>Ischemic optic neuropathy</td>
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<td>Ruiz-Argüelles et al</td>
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<td>Thrombosis at younger than 40/recurrent thrombosis/thrombosis in unusual sites</td>
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<td>Sand et al</td>
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<tr>
<td>Bojalian et al</td>
<td>United States</td>
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<td>1</td>
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<td>Heparin/embolectomy/aspirin</td>
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<tr>
<td>Loeffelbein et al</td>
<td>Germany</td>
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<td>1</td>
<td>Venous and arterial flap thrombosis</td>
<td>Aspirin</td>
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<tr>
<td>Alexandra et al</td>
<td>United States</td>
<td>2011</td>
<td>1</td>
<td>Retinal vein</td>
<td>Aspirin</td>
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<tr>
<td>Gehoff et al</td>
<td>Germany</td>
<td>2011</td>
<td>1</td>
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<tr>
<td>Rac et al</td>
<td>United States</td>
<td>2011</td>
<td>1</td>
<td>Recurrent miscarriage</td>
<td>Aspirin 325 mg/d</td>
</tr>
<tr>
<td>Kotuličová et al</td>
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<td>2012</td>
<td>77</td>
<td>Pulmonary embolism/DVT/MI/acute stroke</td>
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<td>Kubisz et al</td>
<td>Slovakia</td>
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<td>9</td>
<td>2 DVT/4 arterial (acute stroke, MI, arterial thrombosis)/3 both</td>
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<td>Sokol et al</td>
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<td>Darulová et al</td>
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<td>Tekgündüz et al</td>
<td>Turkey</td>
<td>2013</td>
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<td>2013</td>
<td>70</td>
<td>Thrombosis</td>
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</table>

(Continued)
professors Peter Kubisz in Slovakia and Guillermo Ruiz-Argüelles in México.49 We hope that the presentation of this information will result in the development of additional interest in other investigators who could eventually contribute to the better understanding and acceptance of the syndrome, its pathophysiology and treatment, with the goal of helping patients afflicted by thrombophilia, which is currently one of the leading causes of death in developed societies.

Conflicts of Interest
The authors disclose no conflicts of interest.

References

Table 1 (Continued)

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<tr>
<th>Author</th>
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<td>Hayes et al</td>
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<td>Alsheek et al</td>
<td>United States</td>
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<td>Yagmur et al</td>
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<td>Solis-jimenez et al</td>
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<td>Renal allograft rejection (renal infarction)</td>
<td>Nephrectomy/aspin</td>
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</table>

Abbreviations: DVT, deep vein thrombosis; MI, myocardial infarction; t-PA, tissue plasminogen activator.
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