Abstract: Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by recurrent thrombosis, other associated autoimmune disease, and/or obstetrical morbidity along with persistent production of antiphospholipid antibodies. Because of the nature of this systemic disease, most patients are medicated with antithrombotic agents and abundant glucocorticoids. This study reports a cohort of 16 patients with APS, who underwent oral surgery between 2010 and 2017 at the Nagasaki University Hospital. Because oral antithrombotic therapy was continued in the perioperative period, all wounds were strictly closed by suturing to prevent postoperative bleeding. Perioperative laboratory dates and medications were assessed. All patients achieved local postoperative hemostasis and did not exhibit systemic complications. Moreover, there were no postoperative systemic and/or local infections. Oral surgeons should suture oral wounds and ensure local hemostasis to prevent postoperative bleeding. Because patients with APS are likely to develop thrombosis despite continued administration of antithrombotic medications, strict perioperative examination of blood coagulation is needed. Furthermore, it is important to consider the damage and stress caused due to oral surgery. Moreover, when necessary, glucocorticoid therapy should be carefully administered, in accordance with the degree of invasion and judgment of the attending physician.

Keywords: antiphospholipid syndrome; oral surgery; antithrombotic medication; glucocorticoid; postoperative local hemostasis; collagen disease.

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by recurrent thrombosis and/or obstetrical morbidity along with persistent production of antiphospholipid antibodies (aPL) (e.g., lupus anticoagulant, anti-β2-glycoprotein I, and/or anti-cardiolipin antibodies) (1-4). APS is related to one of the most common acquired thrombophilias; however, unlike most genetic thrombophilias, it is associated with both venous and arterial thrombosis (1-4). Moreover, APS can be found in patients with neither clinical nor laboratory evidence of another definable condition; conversely, it may be associated with another disease, mainly systemic lupus erythematous (SLE) and occasionally another autoimmune condition (4), infection (5), drug usage (4), or malignancies (6). In a small subset of patients (less than 1% of all patients with APS), a life-threatening form of APS, known as catastrophic APS, characterized by rapid development of microthrombosis that leads to rapid multiorgan failure, may develop (7,8). Therefore, patients with APS are generally medicated with antithrombotic agents and glucocorticoids. When surgery is performed in these patients, even minor oral surgery, discon-
tinuation of anticoagulant therapy should be avoided to prevent the onset of thrombosis. Previous reports recommend continuing an anticoagulant therapy during tooth extraction to prevent thrombophilia in patients receiving long-term anticoagulant therapy (9-11). Patients with APS also receive high-dose glucocorticoids to control severe polyarthritis; in some patients bisphosphonates are administered to prevent steroidal osteoporosis. Because there are no reports on oral and maxillofacial surgery in patients with APS, the present study reports a cohort of patients with APS who received oral surgery and achieved good postoperative results without any systemic disorders, such as thrombosis.

Materials and Methods

Patients
This retrospective study included 21 cases involving 16 patients with APS who underwent tooth extraction, cystectomy, apicoectomy, and dental implant embedding between April 2010 and July 2017 at the author’s department. All surgeries were performed under local anesthesia, with or without hospitalization. Patients undergoing treatment with oral antithrombotic therapy continued the treatment during the perioperative period. Moreover, other drugs, such as glucocorticoids and bisphosphonates, were continued in the perioperative period. Because all patients had some affiliated disease, disease-related information and dates of laboratory analyses were acquired from medical records. Of the 16 patients, 3 did not undergo a perioperative blood examination. Those patients were followed by other hospitals and medical consultations were performed preoperatively.

Wound suturing
After removal of the oral lesions, all wounds were sutured with 4-0 or 3-0 strings to prevent postoperative bleeding. Absorbable hemostatic agents, such as oxidized cellulose (Surgicel, Ethicon, Somerville, NJ, USA), a gelatin-based agent (Spongol, Astellas, Tokyo, Japan), or a collagen-based agent (Teruplug, Olympus Terumo Biomaterials Corp., Tokyo, Japan) were administered to most patients. Other hemostatic devices, such as electrocauterization or tie-over technique, were not used.

Ethical approval
This study was approved by the Institutional Review Board of the Nagasaki University (Registration number; 18031909).

Results

Patients, laboratory dates, and medications
The median patient age was 52.0 years (range, 33-99 years), with 13 being women and 3 being men. Patients had a history of SLE (9/16, 56.3%), osteoporosis (5/16, 31.3%), lupus nephritis (3/16, 18.8%), thyroid-associated disease (3/16, 31.3%), diffuse scleroderma (2/16, 12.5%), interstitial pneumonia (2/16, 12.5%), mixed connective tissue disease (1/16, 6.3%), Sjögren’s syndrome (2/16, 12.5%), and arteriovenous-associated disease (presenting as subarachnoid hemorrhage, polyarteritis nodosa, deep vein thrombosis, and aortic dissection) (5/16, 31.3%). The clinical diagnosis of oral lesions included periapical periodontitis, periodontitis marginalis, radicular cyst, and tooth loss. Nineteen cases underwent tooth extractions, 1 underwent cystectomy, and 1 underwent embedding of dental implants. The number of extracted teeth ranged from 1 to 13 (Table 1). Most patients had glucocorticoid-associated osteoporosis and interstitial pneumonia.

Of the 16 patients, 10 were perioperatively tested for activated partial thromboplastin time (APTT). The median APTT was 38.4 s (range, 26.3-61.5 s). In addition, the median international normalized ration of prothrombin time (PT-INR) of all patients medicated with warfarin (9 patients) was 1.63 (range, 1.31-2.67). D-dimer levels were preoperatively examined in 3 patients, and all were below 1.0 μg/mL. Hemoglobin, platelets, and liver and kidney function were not substantially altered in any of the patients.

Of the 16 patients, 2 were not specifically treated with antithrombotic agents. Single oral antithrombotic therapy was administered to 7 patients (2, warfarin; 3, aspirin; 1, apixaban; and 1, beraprost), and double oral antithrombotic therapy (warfarin and aspirin) was administered to 6 patients. Sarpogrelate hydrochloride was administered with aspirin to 4 patients, and cilostazol and dipyridamole with warfarin were administered to 2 patients. Glucocorticoids were administered to 14 patients. The median dose of glucocorticoids was 6 mg/day (range, 3-27.5 mg). To eliminate aPL, some patients with APS required immunosuppression (3). Of the 16 patients in this study, 5 were undergoing treatment with immunosuppressive agents (1 received azathioprine, 1 received tacrolimus hydrate and mycophenolate mofetil, 1 received ciclosporin, and 2 received tacrolimus hydrate). To treat glucocorticoid-induced osteoporosis, oral bisphosphonates were administered to 8 patients (3 patients, risedronate; 3 patients, alendronate; and 2 patients, minodronate) (Table 1).
Clinical course
All patients achieved local postoperative hemostasis without systemic complications, such as thrombosis. A local postoperative complication, a dry socket of the lower third molar, was observed in 1 patient. To prevent secondary infection, this patient was administered antibiotic, until the socket was covered with epithelium, and then wound healing was eventually achieved. No postoperative systemic and/or local infections, including medication-related osteonecrosis of the jaw, were

### Table 1  Clinical characteristics of 16 patients in the present study

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Glucocorticoids</th>
<th>Bisphosphonate</th>
<th>Antithrombotic agents</th>
<th>Withdrawal of antithrombotic agents</th>
<th>Immuno-suppressive agents</th>
<th>Preoperative antibiotics</th>
<th>Surgical procedure</th>
<th>Site of surgical association</th>
<th>Number of teeth extracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>64</td>
<td>PSL (5 mg)</td>
<td>No</td>
<td>Risedronate</td>
<td>Wf (3.5 mg), dipyridamole (300 mg)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Ext</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>48</td>
<td>PSL (10 mg)</td>
<td>Risedronate</td>
<td>Asp (100 mg)</td>
<td>Wf (2 mg), Asp (100 mg)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</tr>
<tr>
<td>3</td>
<td>F</td>
<td>52</td>
<td>PSL (6 mg)</td>
<td>Alendronate</td>
<td>No</td>
<td>Wf (2 mg), Asp (100 mg)</td>
<td>No</td>
<td>No</td>
<td>Tacrolimus (4 mg)</td>
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<td>Ext</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>45</td>
<td>PSL (5 mg)</td>
<td>No</td>
<td>Beraprost (20 µg)</td>
<td>Wf (2 mg), Asp (100 mg)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Ext</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
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<td>Risedronate</td>
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<td>Wf (2 mg), Asp (100 mg)</td>
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<td>No</td>
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</tr>
<tr>
<td>6</td>
<td>F</td>
<td>58</td>
<td>PSL (5 mg)</td>
<td>Alendronate</td>
<td>No</td>
<td>Wf (2 mg), Asp (100 mg)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</tr>
<tr>
<td>7</td>
<td>M</td>
<td>53</td>
<td>PSL (5 mg)</td>
<td>No</td>
<td>Aripixaban (5 mg)</td>
<td>Wf (2 mg), Asp (100 mg)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Ext</td>
</tr>
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<td>8</td>
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<td>Asp (81 mg)</td>
<td>Wf (2 mg), Asp (100 mg)</td>
<td>No</td>
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<td>9</td>
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<td>67</td>
<td>PSL (12.5 mg)</td>
<td>Minodronate</td>
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<td>No</td>
<td>Asp (100 mg)</td>
<td>Wf (2 mg), Asp (100 mg)</td>
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<td>No</td>
<td>No</td>
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<tr>
<td>12</td>
<td>F</td>
<td>55</td>
<td>PSL (8 mg)</td>
<td>No</td>
<td>Wf (3 mg), dipyridamole (200 mg)</td>
<td>Wf (2 mg), Asp (100 mg)</td>
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<td>No</td>
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<td>No</td>
<td>Ext</td>
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<tr>
<td>13</td>
<td>F</td>
<td>65</td>
<td>–</td>
<td>No</td>
<td>Asp (100 mg), sarpogrelate hydrochloride (300 mg)</td>
<td>Wf (2 mg), Asp (100 mg)</td>
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<td>No</td>
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<td>14</td>
<td>F</td>
<td>41</td>
<td>–</td>
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<td>No</td>
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<td>No</td>
<td>No</td>
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</tr>
<tr>
<td>15</td>
<td>F</td>
<td>27</td>
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<td>No</td>
<td>No</td>
<td>Wf (3 mg), dipyridamole (300 mg)</td>
<td>No</td>
<td>No</td>
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<tr>
<td>16</td>
<td>F</td>
<td>47</td>
<td>PSL (20 mg)</td>
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<td>Wf (3 mg), dipyridamole (300 mg)</td>
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<td>No</td>
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<td>17</td>
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<td>Asp (100 mg), sarpogrelate hydrochloride (300 mg)</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Ext</td>
</tr>
</tbody>
</table>

PSL: Prednisolone; Wf: warfarin; Asp: aspirin; AMPC: amoxicillin; Ext: extraction.
detected in any of the patients.

Discussion
The incidence of APS is approximately 5 new patients per 100,000 individuals per year, and the prevalence is approximately 40-50 patients per 100,000 individuals (4). The involvement of aPL is clinically important for normal procoagulant and anticoagulant reactions, and in certain cells, altered expression and secretion of various molecules serves as the basis for possible mechanisms underlying the development of thrombotic events in patients with APS (12,13). Because of the low number of patients with APS, surgical procedures, especially for oral and maxillofacial lesions in such patients, had never been reported. To date, there have been some reports regarding heart valve surgery (14,15), cardiovascular surgery (16), and organ transplantation (17) in patients with APS. In the present study, antithrombosis in patients with APS was well controlled, and no thrombotic events were demonstrated in the perioperative period. However, 2 patients were not treated with antithrombotic medications. In general, patients with APS who experience an initial venous thrombosis event should receive oral anticoagulant therapy with warfarin to achieve a target PT-INR of 2.0-3.0 (18). It is controversial whether patients with definite APS and arterial thrombosis should receive oral anticoagulant therapy to achieve a target PT-INR of approximately 3.0, or whether they should receive combined therapy of antiaggregant and anticoagulant to achieve a target PT-INR of 2.0-3.0 (18). In the present study, the median PT-INR of all patients who received warfarin was 1.63 (range, 1.31-2.67), indicating that antithrombotic therapy alone might be slightly insufficient. Moreover, Miyatani and colleagues reported that antithrombotic therapy alone might be slightly insufficient when a patient is administered anticoagulant drugs, other than warfarin. Based on this retrospective study, although not all patients were evaluated with regard to APTT, preoperative APTT evaluation in patients with APS was needed in the future, and that this examination will improve safety and certainty regarding postoperative hemostasis. Because there are sometimes patients with nonsymptomatic APS, blood coagulation checks during preoperative systemic examinations are also essential, especially in patients with collagen disease, such as SLE, mixed connective tissue disease, vasculitis syndrome, rheumatoid arthritis, and Sjögren’s syndrome (19).

Patients with APS are frequently medicated with glucocorticoid to control organ-related symptoms. Because the use of glucocorticoid increases a patient’s susceptibility to infection, oral surgeons should ensure infection control at the surgical site via appropriate administration of antibiotics, local lavage of the wound, and the improvement of oral hygiene. In this study, the median glucocorticoid dose was 6 mg per day and antibiotics were preventively administered in all patients. Friedman and colleagues reported that 28 patients, who had taken an average of 10 mg prednisolone daily for 7 years, underwent major orthopedic operations without any increase in steroid dosage (20). Clinical observations and laboratory measurements were not suggestive of adrenocortical insufficiency. Those investigators asserted that the doses of glucocorticoids higher than physiological levels are unnecessary to meet the demands of operative stress in patients on glucocorticoid therapy (20). Thus, the damage and stress caused by surgery might be evaluated in preoperative consultation with a medical specialist in internal secretion.

In conclusion, APS is a complex disease that requires careful treatment with antithrombotic agents during the perioperative period. Oral surgeons should suture oral wounds and ensure local hemostasis as much as possible. Because patients with APS exhibit the potential for the development of thrombosis, despite continuation of antithrombotic medications, strict examination of blood coagulation is necessary, particularly in the surgical perioperative period. Moreover, when necessary, glucocorticoid therapy should be carefully administered, in accordance with the degree of invasion and judgment of the attending physician.

Conflict of interest
The authors declare that they have no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References


