



Case report

Association between impaired healing after orthognathic surgery and irritable bowel syndrome: A case report and literature review

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ABSTRACT

Introduction: In the disease irritable bowel syndrome (IBS), gastrointestinal function is worsened even though no organic abnormalities are observed in the gastrointestinal mucosa. We report the case of an orthognathic surgery patient with suspected irritable bowel syndrome.**Case:** In September 2017, a 15-year-old Japanese female was referred to us with dental crowding, malocclusion, and mandibular protrusion. In June 2019, a disagreement with classmates led to abdominal pain, diarrhea, and hemorrhage; in August 2019, a preoperative blood test showed sudden anemia, and her surgery was thus postponed. Subsequent upper and lower gastrointestinal endoscopy revealed no organic abnormality, and no definitive diagnosis was made. In March 2020, after an improvement in anemia was observed, a segmental Le Fort I osteotomy and bilateral sagittal split ramus osteotomy (BSSRO) were performed under general anesthesia. On the third post-operative day, due to the mucosal dehiscence adjacent to the suture part, the titanium plate was exposed, and irrigation of the wound with normal saline solution and oral hygiene instruction was continued daily for 2 weeks. Two years and eight months have passed since the surgery, and the healing of the oral mucosa and bone has been uneventful.**Discussion:** The relationship between IBS and post-operative impaired healing associated with the fragility of the oral mucosa is unknown. However, psychological stress has been reported as a cause of IBS and to be related to oral microorganisms.**Conclusion:** Reducing risk factors for IBS and maintaining proper perioperative oral hygiene is essential in managing similar cases.

1. Introduction

The functional gastrointestinal diseases IBD (inflammatory bowel disease) and IBS (irritable bowel syndrome) are chronic and debilitating [1,2]. The gastrointestinal function of individuals with IBS is impaired and characterized by chronic, recurrent abdominal pain or discomfort and altered bowel habits, even though no organic abnormalities are observed in the gastrointestinal mucosa [3–5]. Based on the severity of the disease, patients with IBS may require medical care from general practitioners, gastroenterologists, and psychosomatic/psychiatry

specialists, particularly if the patients have deep-rooted psychosocial problems [6]. The etiology of IBS remains unclear, but it is suspected to be multifactorial [3,7]. The pooled prevalence of IBS in the 260,960 subjects varied, ranging from 7 % to 21 %, with the highest and lowest prevalence rates in South America and Southeast Asia, where women had a slightly higher risk of IBS than men [8,9]. IBS is also the predominant gastrointestinal problem in Asia.

The diagnosis of IBS is often confusing because its clinical symptoms are challenging to diagnose. Recent research suggests that IBS also has several implications, including an altered immune system, risk of bone

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fracture, and impaired wound healing [10–13]. Interestingly, Wongtrakul et al. reported an increased risk of osteoporosis and osteoporotic fractures in IBS patients. Regarding the evidence of an association between IBS and osteoporosis/osteoporotic fractures, the suspected high-risk mechanisms include chronic inflammatory states, hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, smoking, and nutritional deficiencies [14].

Several studies have also linked IBS to dysbiosis of the human microbiome [15,16]. This dysbiosis is increasingly recognized through mechanisms such as alterations in gut barrier function, triggering or exacerbating inflammation, and the regulation of energy metabolism [17,18]. Like the gut, the mucosal or skin microbiota is thought to play an essential role in mucosal defenses and to have the potential to modulate mucosal immune function and wound healing [19–24].

Research on the relationship between IBS and wound healing is limited. Balikji et al. reported that after severe IBS complaints and significantly decreased immune fitness, IBS patients described slow wound healing [10]. We report an interesting case of a patient with suspected irritable bowel syndrome who underwent orthognathic surgery; she exhibited slowly post-operative wound healing. We also summarize our review of the literature concerning the implications of IBS related to wound healing and fracture.

2. Case presentation

In September 2017, a 15-year-old Japanese female was referred to our clinic with the chief complaints of dental crowding, malocclusion, and mandibular protrusion. The general examination showed her height and weight were 152 cm and 41.0 kg, respectively. A visual inspection revealed mandibular protrusion and deviation of the left chin and right maxilla, concave-type facial profile (Fig. 1A). An intraoral examination revealed a Class III malocclusion with stenosis of the maxilla and mandible arch (Fig. 1B). No remarkable abdominal findings were observed in the temporomandibular joint or its surrounding tissue by panoramic X-ray (Fig. 1C).

The patient's oral hygiene was extremely poor. The representative initial cephalometric measurements were performed using WinCeph ver. 11 (Rise Corporation, Japan), a patient communication tool in orthodontic dentistry, with averaged comparisons from Japanese female cephalometric values (Table 1). Sella-nasion (SN) to point A angle (SNA): 81.7° (mean 81.5°, standard deviation [SD] 4.2°), SN to point B (SNB): 86.7° (mean 77.1°, SD 3.8°), A point-nasion-B point (ANB): -5.0° (mean 4.4°, SD 0°), the angle between the mandibular plane and the Frankfort plane (Mp-FH): 27.5° (mean 34.0°, SD 3.8°), gonial angle: 128.4° (mean 131.0°, SD 5.6°), the angle between the upper incisor axis to the SN (U1-SN): 118.1° (mean 105.4°, SD 5.2°), the angle between the upper incisor to the nasion-A-point (NA) line (U1-NA): 36.5° (mean 24.7°, SD 5.2°), the angle between the axial inclination of the mandibular central incisor and the mandibular plane (L1-Mp): 82.2° (mean 95.4°, SD 6.3°), the angle between the lower incisor to the nasion-B-point (NB) line (L1-NB): 17.3° (mean 31.0°, SD 6.6°), the angle between the upper incisor axis and the lower incisor axis (IIA): 131.2° (mean 118.7°, SD 7.5°), the angle between the SN and the occlusal plane (Occ P): 10.3° (mean 20.2°, SD 3.5°), the Frankfort mandibular plane angle (FMA): 27.5° (mean 28.8°, SD 5.2°), the angle between the axis of the lower incisor and the mandibular plane (IMPA): 82.2° (mean 96.3°, SD 5.8°), Frankfort mandibular incisor angle (FMIA): 70.3°, the distance from the upper incisor to the NA line (U1/NA): 8.8 mm (mean 6.2 mm, SD 1.9 mm), the distance from the lower incisor to the NB (L1/NB): 3.9 mm (mean 7.8 mm, SD 2.4 mm), and the distance from the pogonion to the NB (Pog/NB): 1.1 mm (mean 0.4 mm, SD 1.2 mm).

The clinical diagnosis was skeletal class III malocclusion, a jaw deformity with facial asymmetry, and constricted dental arch. Preoperative orthodontic treatment was started to make teeth in a proper alignment, but the patient was not brushing her teeth at all and was seen monthly for oral hygiene instruction. In June 2019, she had a

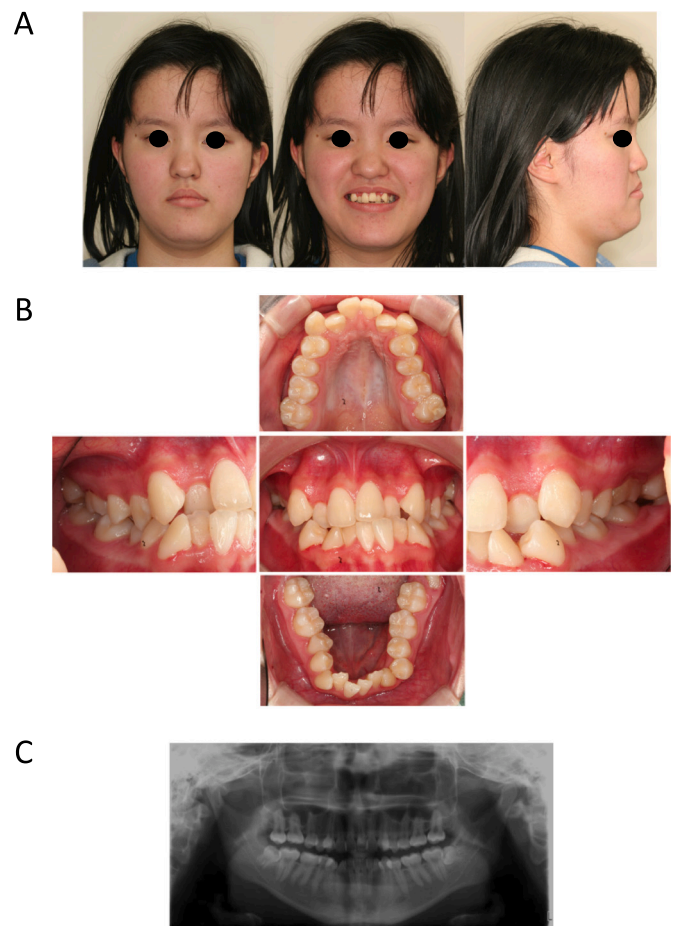


Fig. 1. Extraoral and intraoral photographs and panoramic X-rays at the first visit of the patient, a 15-year-old Japanese female. A: Extraoral photographs. B: Intraoral photographs. C: panoramic X-ray.

disagreement with her classmates, and immediately after that she began to have diarrhea, felt abdominal pain/discomfort, and reported persistent melena which exacerbated her original hemorrhoids and led to continuous bleeding. The family physician suspected ulcerative colitis and referred the patient to a gastroenterologist, but due to the patient's circumstances she did not go to the gastroenterologist.

After the patient's preoperative orthodontic treatment, the patient visited our clinic in July for blood storage and orthognathic surgery was planned for August 2019. However, the orthognathic surgery was postponed because at that point (i) the patient's hemoglobin (Hb) had decreased from 12.5 g/dL to 10.2 g/dL in approx. 1 month, (ii) it was difficult to achieve 400 mL of stored blood, and (iii) the patient had not seen a gastroenterologist. Her preoperative blood test data compared to the initial examination were as follows. Total protein (TP): 7.6 → 5.9 g/dL, serum iron (Fe): 117 → 16 µg/dL, C-reactive protein (CRP): 0.10 → 0.31 mg/L, white blood cells (WBC): 6500 → 12,200/µL, Hb: 15.7 → 10.2 g/dL, and hematocrit (Hct): 45.9 → 32.5 %.

In June 2019, an upper and lower gastrointestinal endoscopy was performed by a gastroenterologist for an assessment of the patient's upper and lower gastrointestinal tracts, but no organic changes were observed. No definitive diagnosis was obtained from the gastroenterologist. Fig. 2 provides extraoral (Fig. 2A) and intraoral (Fig. 2B) photographs after the patient's pre-surgical orthodontic treatment.

In March 2020, after 7 months of follow-up and a preoperative 400-mL blood storage, the patient (under general anesthesia) underwent a segmental Le Fort I osteotomy (posterior impaction and widening by 5 mm) and bilateral sagittal split ramus osteotomy (BSSRO)(8 mm setback). The pre-operative values were TP: 7.4 g/dL, Fe: 29 µg/dL, CRP:

Table 1
Cephalometric measurement based on Steiner and Tweed analysis.

	Mean	SD	Initial (15 yrs, 7 m)	Pre-treatment (18 yrs, 1 m)	Post-treatment (19 yrs, 10 m)
Angular analysis, degree					
SNA	81.5	4.2	81.7	82.7	80.6
SNB	77.1	3.8	86.7	87.3	82.9
ANB	4.4	0.0	-5.0	-4.5	-2.2
Mp-FH	34.0	3.8	27.5	27.0	27.1
Gonial angle	131.0	5.6	128.4	126.7	129.5
U1-SN	105.4	5.2	118.1	102.0	116.1
U1-NA	24.7	5.2	36.5	19.3	35.5
L1-Mp	95.4	6.3	82.2	89.2	90.3
L1-NB	31.0	6.6	17.3	23.4	21.3
IIA	118.7	7.5	131.2	141.9	125.4
Occ P	20.2	3.5	10.3	13.4	8.9
FMA	28.8	5.2	27.5	27.0	27.1
IMPA	96.3	5.8	82.2	89.2	90.3
FMIA	54.6	6.5	70.3	63.8	62.6
Linear analysis, mm					
U1/NA	6.2	1.9	8.8	4.2	7.8
L1/NB	7.8	2.4	3.9	4.9	4.5
Pog/NB	0.4	1.2	1.1	3.0	3.9

Mean: Average values of Japanese women. A: A-point, B: B-point, FMA: Frankfort mandibular plane angle, FMIA: Frankfort mandibular incisor angle, Gonial angle: angle between ramus plane and mandibular plane, IIA: angle between upper incisor axis and lower incisor axis, IMPA: the angle between the axis of lower incisor and mandibular plane, L1/NB: distance from lower incisor to NB, L1-Mp: angle between the axial inclination of mandibular central incisor and mandibular plane, L1-NB: the angle between lower incisor to nasion-B-point (NB) line, Mp-FH: angle between mandibular plane and Frankfort (FH) plane, N: nasion, Occ P: the angle between SN and occlusal plane, Pog/NB: distance from pogonion to NB, S: sella, SD: standard deviation, SN: sella-nasion plane, U1/NA: distance from upper incisor to NA, U1-NA: the angle between upper incisor to nasion-A-point (NA) line, U1-SN: upper incisor axis to SN.

0.05 mg/L, WBC: 5600/μL, Hb: 11.6 g/dL, and Hct: 37.2 %. Intra-operatively, the mucosa was fragile at the site where the retractor touched.

On the third post-operative day, due to the mucosal dehiscence adjacent to the suture part of the right maxilla (Fig. 3A), left maxilla (Fig. 3B), and left mandible (Fig. 3C), the titanium plate was exposed, and irrigation of the wound with normal saline solution and oral hygiene instruction was continued daily for 2 weeks. A biopsy of the area where the mucosa was dissected revealed no characteristic histopathological findings; the tissue was composed of fibrous connective tissues with mild chronic inflammation and lined by parakeratinized stratified squamous epithelium (Fig. 4).

At 3 weeks postoperatively, the sequester was recognized at the bone on the medial side of the maxillary right central incisor, and the exposure of the apatite block used to maintain the widening of the maxillary expansion was observed (Fig. 3D). The apatite block and the sequester were then removed under local anesthesia (Fig. 3E). The 1-week post-operative panoramic X-ray and CT horizontal sections presented in Fig. 5A and B indicate the area where the width diameter of the maxilla was enlarged.

At 2 weeks postoperatively, the patient experienced abdominal pain, diarrhea, and bloody stools; she visited her family physician, who prescribed medications to control the patient's bowel function. Approximately 6 months later, the patient's watery diarrhea had continued and her weight had dropped to 34 kg. In September 2020, the patient was diagnosed with a depressive state but continued to take a leave of absence; her health then improved greatly and her weight recovered to 40 kg. However, in August 2021, the patient still had persistent watery stools, bloody bowel discharge, and her weight had decreased to 33 kg; an urgent lower gastrointestinal examination was thus conducted, and based on its findings the patient was diagnosed with ulcerative colitis.

One year and eight months after the segmental Le Fort I osteotomy and BSSRO, bone formation was confirmed at the site of segmental maxillary expansion (Fig. 5C), the jaw deformity and facial asymmetry were corrected (Fig. 6A), and the oral mucosa and the stability of the occlusion had been maintained; normal healing and good progress were observed (Fig. 6B). The representative preoperative cephalometric values were improved as follows (Table 1). SNA: 82.7° → 80.6°, SNB: 87.3° → 82.9°, ANB: -4.5° → -2.2°, Mp-FH: 27.0° → 27.1°, Gonial angle: 126.7° → 129.5°, U1-SN: 102.0° → 116.1°, U1-NA: 19.3° → 35.5°, L1-Mp: 89.2° → 90.3°, L1-NB: 23.4° → 21.3°, IIA: 141.9° → 125.4°, Occ P: 13.4° → 8.9°, FMA: 27.0° → 27.1°, IMPA: 89.2° → 90.3°, FMIA: 63.8° → 62.6°, U1/NA: 4.2 mm → 7.8 mm, L1/NB: 4.9 mm → 4.5 mm, and Pog/NB: 3.0 mm → 3.9 mm. This case has been reported according to the SCARE 2020 criteria [25].

3. Discussion

When performing orthognathic surgery, it is necessary not only to focus on jaw distortion and facial asymmetry based on the patient's chief complaints but also on the patient's background and a comprehensive systemic examination. Although the present patient was suspected of having IBS, a definitive diagnosis was not reached by the pre-operative consultation. This might have occurred because the clinical symptoms of IBS vary among patients, and both patients and clinicians often regard the symptoms as an inflammatory bowel disease (IBD; including Crohn's disease and ulcerative colitis) or a "non-existent diagnosis." In our patient's case, the impaired mucosa and bone healing after orthognathic surgery also contributed to the difficulty in diagnosis.

The direct relationship between IBS and post-operative impaired healing associated with the fragility of the oral mucosa is not clearly understood. We hypothesized that gastrointestinal health (including IBS) and psychological stress could affect post-surgical healing. The clinical implications of IBS with altered immune function and impaired wound healing have been discussed [10,26]. We conducted a literature review of studies related to the association of IBS with the immune

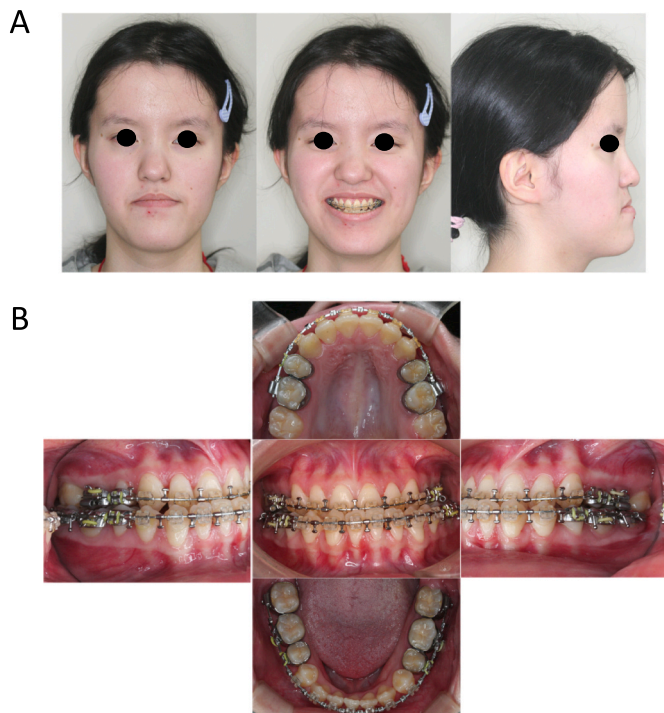


Fig. 2. Extraoral and intraoral photographs after preoperative orthodontic treatment. A: Extraoral photographs. B: Intraoral photographs.

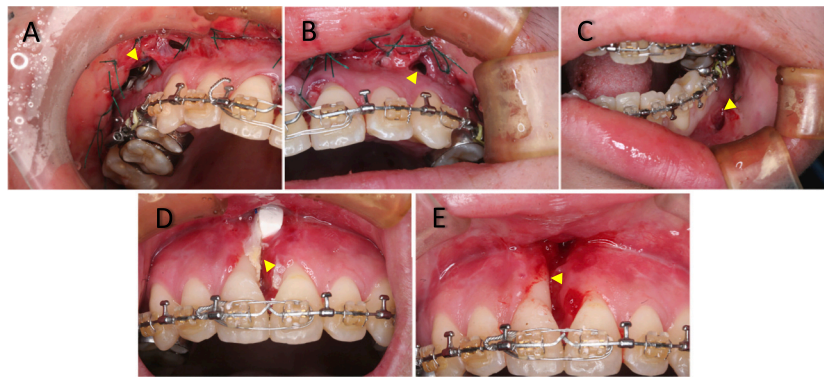


Fig. 3. Post-operative clinical intraoral photographs. A–C: On the third post-operative day. A: The plate was exposed due to the mucosa adjacent to the sutured region being ruptured (arrowhead) on the right side (A) of the maxilla, left side (B) of the maxilla, and the left of the mandibular molar region (C). D: At 1 month later, congenital sequestration (arrowhead) and apatite block appeared. E: After the removal of the sequester and the apatite block.

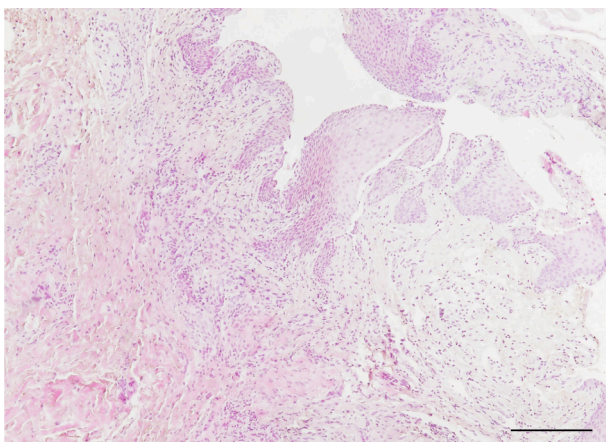


Fig. 4. Hematoxylin and eosin (HE) staining of oral mucosal lacerations. Bar, 200 μ m.

system, risk of fracture, and impaired wound healing (Table 2). Cremon et al. reported that total immune cells, most of which are mast cells known to be important in host defense, were increased in IBS patients [27]. It was also indicated that the relationship between gut microbiota and altered immune function is associated with genetic polymorphisms in patients with IBS, leading to reduced expressions of transporters and reduced serotonin reuptake, which terminates serotonin action and leads to IBS symptoms [26,28].

Balikji et al. reported a significant association among IBS, altered immune function, and impaired wound healing due to intestinal dysbiosis [10]. Several studies have indicated that IBS patients are at increased risk of osteoporosis and related fractures due to the use of inflammatory mediators and selective serotonin receptor inhibitors (SSRIs) [11,13,29].

The present case report is interesting because it is the first to describe an association between the impaired wound and bone healing of orthognathic surgery and IBS. This patient's case implies the need for a multidisciplinary approach for dealing with similar cases. Our patient's IBS was suspected to be triggered by psychological stress due to disagreement with a classmate, complex homework, absenteeism, and her facial profile. This is supported by a study by Qin et al. indicating that psychological stress has a marked impact on intestinal activity and vice versa [30]. Chen et al. studied female students and showed that several risk factors influenced IBS, such as dysmenorrhea, food avoidance, and class absences. The students who were absent >3 days/semester were 1.8 times more at risk of developing IBS compared to those who were not absent >3 days/semester. School-related stressors include

school assignments, teacher-student interactions, the availability of part-time jobs, the number of credits for school study, future career plans, and more. Alleviating the discomfort of IBS, identifying stress-related factors, and improving these factors would help reduce the incidence of IBS [31]. In addition, therapeutic interventions—both pharmacologic and nonpharmacologic—targeting the brain-gut axis can relieve debilitating symptoms of IBS [30,32].

In the present patient, stress reduction was also necessary. The progression of IBS to ulcerative colitis at 6 months postoperatively, a hallmark of IBD in this patient's case, is one of the important findings. The relationship between IBS and IBD is well recognized. The relative risk of IBD was reported to be 15.7 times higher among patients with antecedent IBS compared to those without a history of IBS [33]. In another study, the relative risk of a change from IBS to IBD was 16.3 higher in patients with IBS, possibly due to mental stress [34].

Our patient also showed mucosal opening and necrosis around the maxillary midline, a sign of impaired wound healing, at 3 weeks after her orthognathic surgery. The cause of healing failure in this case remains unknown, but systematic changes may have induced mucosal fragility during the immune and healing processes (especially connective tissue abnormalities). Clinically, changes in the gut microbiome significantly alter chronic wound healing [10]. An investigation using mice showed conversions in the gut microbiota due to administration of the antibiotic vancomycin, which also contributed to wound dysbiosis and impaired wound healing [35]. Changes in skin integrity in mice lead to gut dysbiosis and vice versa [36,37]. In humans, subsequent IBS-like signs and symptoms can lead to decreased mood and impaired cognitive function. The resulting gut dysbiosis can lead to psychological distress in a background of depression and anxiety, which can significantly impair an individual's quality of life, perceived health, and immune fitness, and it can complicate treatment strategies [10].

Successful periodontal treatment or oral health maintenance can improve endothelial function and systemic inflammation associated with non-oral diseases, including IBS [38]. IBS patients must pay close attention to their oral health and oral health-related attitude [39]. The present patient had significantly poor preoperative oral hygiene management which did not improve despite regular tooth brushing instruction, and she required continuous daily oral cleaning by an oral surgical hygienist after her surgery and then intervention by a hygienist at the patient's orthodontic clinic after discharge. Oral disease and its various related factors are significantly associated with the pathology and severity of IBS, as seen in the effects of oral disease and gastrointestinal disorders including *H. pylori* infection, peptic ulcers, constipation, diarrhea, and dyspepsia [40–42]. To reduce the severity of IBS, it is necessary to avoid poor oral hygiene. We therefore stress the maintenance of adequate perioperative oral hygiene in patients suspected of having IBS.

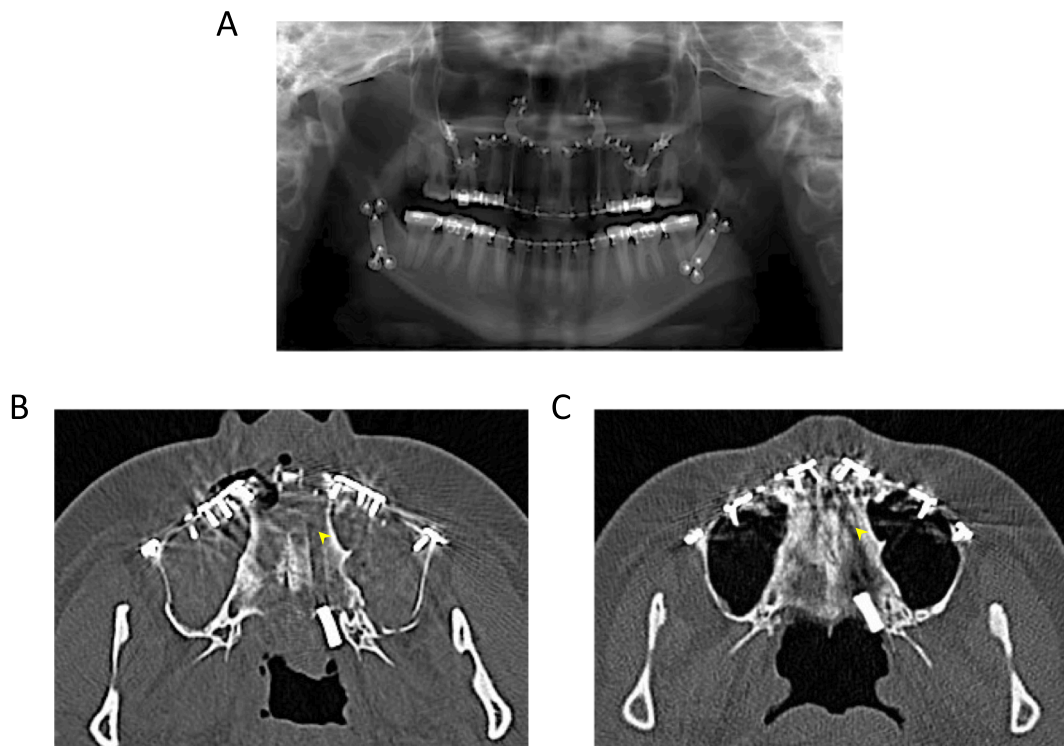


Fig. 5. Radiographic examination after surgery. A: A panoramic X-ray taken 1 week after surgery. B and C: CT images at the site of segmental maxillary expansion (arrowhead) at 4 days (B) and 1 year 8 months (C) after surgery.

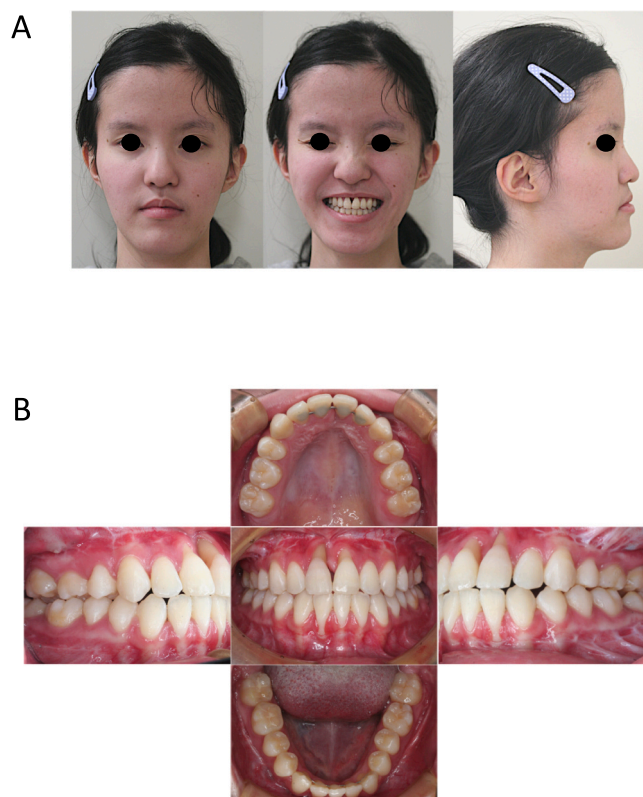


Fig. 6. Extraoral and intraoral photographs and panoramic X-ray at debonding. A: Extraoral photographs. B: Intraoral photograph.

A limitation of our study is the lack of findings concerning direct effects of gut microbiome on IBS and impaired wound and bone healing. Further research regarding this topic is necessary.

4. Conclusion

This is the first report of a case of a patient who underwent orthognathic surgery and was suspected of having IBS. A definitive diagnosis of IBS should be made carefully during the pre-operative consultation. We emphasize that a comprehensive assessment is required prior to orthognathic surgery. Reducing risk factors for IBS and maintaining proper perioperative oral hygiene is essential in the management of similar cases.

Source of funding

None to declare.

Ethical approval

Our institution exempted ethical approval.

Consent

Written informed consent was obtained from the patient to publish the case report and accompanying images. Identifiable patient information has been removed.

Registration of research studies

Not applicable.

Guarantor

Kazuki Akizuki and Tsuyoshi Shimo

Table 2
Several studies linked IBS to fracture risk, the immune system, and impaired wound healing.

Author	Year	[ref. no.]	Country	Study design	Recruitment of participants	Outcomes	Findings
Cremon	2009	[27]	Italy	nRCT	48 IBS; 24 non-IBS	Number of immune cells in IBS patients	Total immune cells in IBS patients increase (71.8 %); Significant correlation between mast cell & frequency of bloating; Negative correlation between CD8+ T cells & abdominal discomfort.
Kodani	2018	[43]	Japan	In vitro study	6 mice DSS-induced colitis (a model for IBS after acute colitis)	Immune cells in mice IBS-models	MR-positive macrophage was increased in the muscular layer two weeks after DSS-induction; Tryptase-positive cells were more significant in a mucosal and muscular layer at 4–12 weeks after DSS-induction.
Lee	2018	[13]	Taiwan	Cohort study	29,505 subjects (IBS & n-IBS) selected from database	Risk of fracture; incidence of IBS	IBS group has an increased risk of fracture
Balikji	2021	[10]	Netherlands	Observational study	1942 subjects complete the online survey	Altered immune function and impaired wound healing in IBS patients	236 IBS patients reported impaired wound healing; The negative association between impaired wound healing and perceived immune fitness.
Lee	2021	[11]	Korea	Retrospective cohort	7725 subjects (IBS & n-IBS) selected from database	Risk of osteoporosis & osteoporotic fracture; incidence of IBS	Increased incidence of osteoporosis & osteoporotic fracture in female IBS patients.

nRCT: non-randomized clinical trial, IBS: irritable bowel syndrome, n-IBS, non-irritable bowel syndrome.

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CRediT authorship contribution statement

All authors contributed equally to this case report's data collection, analysis and interpretation, and writing.

Declaration of competing interest

The authors report no conflicts of interest regarding this paper.

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