Journal of Interdisciplinary Medicine

Volume 7 // Issue 2 // June 2022

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Journal of Interdisciplinary Medicine

REVIEW

INFECTIOUS DISEASES // EPIDEMIOLOGY // PUBLIC HEALTH

Mucormycosis in the COVID-19 Era – A Natural Calamity or Man-Made Disaster? Current Evidence and Review of the Literature

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ARTICLE HISTORY

Received: April 30, 2022
Accepted: June 26, 2022

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ABSTRACT

Mucormycosis is a potentially fatal disease caused by a fungus of the order Mucorales, most commonly involving the nasal sinuses, orbits, brain, lungs, and skin. The disease affects mostly immunosuppressed individuals and patients with chronic diseases such as diabetes. The prevalence of mucormycosis is 80 times higher (0.14 per 1000) in India compared to developed countries. Since the outbreak of the COVID-19 pandemic, there has been a sudden surge in the number of mucormycosis cases, especially on the Indian subcontinent. This can be attributed to what we consider to be the perfect iatrogenic recipe: a combination between the immunosuppression caused by COVID-19, the large prevalence of uncontrolled diabetes and the simultaneous use of corticosteroids. Other factors include the excessive use of antibiotics, antifungal drugs and zinc supplements, invasive ventilation, poor hygiene and sanitization as well as the use of industrial oxygen in hospitals. As a result, an overwhelmingly large number of COVID-19 patients have developed mucormycosis during the pandemic. A review of the literature suggests that all efforts should be made to keep tight control of glycemia in COVID-19 patients along with judicious use of corticosteroids. The treatment of mucormycosis involves a combination of medical and surgical therapy, with the early initiation of antifungal drugs and aggressive surgical debridement of the affected tissues.

Keywords: mucormycosis, COVID-19, diabetes mellitus, corticosteroids

INTRODUCTION

Mucormycosis is a potentially fatal disease that commonly involves the nasal sinuses, orbits, brain, lungs, and the skin. Rarely, it can even cause disseminated disease. Mucormycosis is caused by a fungus of the order Mucorales, subphylum Mucormycotina. It is highly invasive and relentlessly progressive, resulting in high rates of mortality. The worldwide prevalence of mucormycosis varies from 0.005 to 1.7 per million. In contrast, its prevalence is an astounding 80

times higher (0.14 per 1,000) in India compared to developed countries.[1,2] Put simply, India is the world capital of mucormycosis. Since the outbreak of the COVID-19 pandemic, there has been a sudden surge in the number of mucormycosis cases, especially on the Indian subcontinent. Some other countries, such as Mexico and Russia, also reported an increased incidence of mucormycosis after the COVID-19 outbreak.

MYCOLOGY

Mucormycosis is caused by fungi belonging to the *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella*, and *Absidia* species. These organisms are present everywhere in nature and are commonly seen in decomposing vegetation in the soil.[3] They breed promptly and release an enormous number of spores, which rapidly become airborne and are transported on long distances. Due to their ubiquitous presence in the environment, the majority of humans have significant exposure to these fungi during their everyday life. However, the fungi seldom cause an infection in humans with a healthy immune system, and the majority of cases occur in an immunocompromised host. The hyphae of these species have a trenchant appearance that helps in the identification of clinical specimens. The hyphae appear thick (5–15 μm diameter) with irregular branching patterns and no septations.

PATHOGENESIS

The disease is acquired through the inhalation of spores. In healthy individuals, the spores are cleared through the gastrointestinal tract. In immunosuppressed individuals, the initial infection starts in the nasal turbinates or the alveoli.[4] The fungi are angio-invasive, leading to infarction of the infected tissues.[5]

There are several factors that increase the risk of mucormycosis. One of them is deferoxamine therapy, which chelates iron and enhances the risk of mucormycosis by accelerating the growth of fungi.[6–8] The deferoxamine-iron chelate, called feroxamine, is a siderophore for the *Rhizopus* species, increasing iron uptake by the fungus, which stimulates fungal growth and leads to tissue invasion.[9] Iron overload independently stimulates the growth of fungi even in the absence of deferoxamine therapy. Also, mucormycosis-causing organisms have a special enzyme called ketone reductase, which helps them to survive in hostile conditions such as high-glucose and acidic environments. A healthy immune system suppresses the growth of mucormycosis-causing organisms, whereas in patients with diabetic ketoacidosis, the growth of *Rhizopus* is accelerated because of this special enzyme.[10] Even in the absence of ketoacidosis, hyperglycemia can directly contribute to the risk of mucormycosis by at least one of the following mechanisms:

- hyperglycation of iron – sequestering proteins, disrupting normal iron sequestration;
- upregulation of a mammalian cell receptor (GRP78) that binds to Mucorales, enabling tissue penetration;
- induction of poorly characterized defects in phagocytic function;
- enhanced expression of cotH, a Mucorales-specific protein that mediates host cell invasion by binding to GRP78 due to hyperglycemia and the resulting free iron.

Risk factors for mucormycosis include:

- diabetes mellitus, particularly when associated with ketoacidosis;
- glucocorticoid treatment;
- hematologic malignancies and hematopoietic cell transplantation;
- solid organ transplantation;
- deferoxamine treatment and iron overload;
- AIDS;
- injection drug use;
- trauma/burns;
- malnutrition.

THE POSTULATED MECHANISM FOR THE SURGE OF MUCORMYCOSIS CASES DURING THE COVID-19 PANDEMIC

SARS-CoV-2 causes lower respiratory tract infection and acute respiratory distress syndrome (ARDS). Besides the diffuse alveolar damage with severe inflammatory exudation, COVID-19 patients also have immunosuppression with a decrease in CD4 and CD8 T cells.[11] A study conducted in 2020 observed that critically ill patients, who were admitted to the intensive care unit (ICU) and required mechanical ventilation or had a longer duration of hospital stay, were more likely to develop fungal co-infections.[12] Other studies have also come to the conclusion that COVID-19 patients can develop fungal infections during the middle and even the later stages of the disease.[13] The number of patients who developed post-COVID mucormycosis was overwhelming. Upon retrospec-

tive analysis of the available data, we observed that the perfect iatrogenic recipe was cooked, which gave birth to a mucormycosis endemic in an ongoing COVID-19 pandemic. Some of the factors that contributed to this surge are listed below.

1. **The very large number of patients with diabetes and prediabetes.** India is the world capital of diabetes; every seventh Indian has either diabetes or prediabetes. According to a study published in The Lancet in 2017, the overall prevalence of diabetes in 15 states of India is 7.3% (95% CI 7.0 to 7.5), with higher levels in urban areas (11.2%, 95% CI 10.6 to 11.8) compared to rural areas (5.2%, 95% CI 4.9 to 5.4).[14] The majority of the population has poor glycemic control, putting them at high risk of mucormycosis. According to a study, 97% of patients who had post-COVID rhino-orbital mucormycosis were diabetic.[15] Another study showed that uncontrolled diabetes was present in 93% of patients who developed rhino-orbital-cerebral infection.[16]
2. **Excessive use of corticosteroids.** The second wave of COVID-19 in India was caused by the Delta strain, which was notorious for severe disease and ARDS. Thus, the number of patients who required corticosteroid treatment was very high. Steroids unmasked the diabetes of this large population and worsened their glycemia, putting them at risk of mucormycosis. According to one study, 80% of patients who had post-COVID rhino-orbital mucormycosis had received steroid treatment.[16]
3. **Unnecessary use of antibiotics.** The majority of the Indian population took unnecessary antibiotics ranging from macrolides to carbapenem, which disturbed their normal flora, predisposing them to mucormycosis.[17]
4. **Unnecessary use of antifungal drugs for prophylaxis.** It has been noted that many centers were using voriconazole for fungal prophylaxis, which increased the risk for mucormycosis.[18] As observed in one study, 6% of patients who developed mucormycosis in India had been given voriconazole for fungal prophylaxis.[16]
5. **Invasive ventilation.** A systematic review of the literature has shown that invasive mechanical ventilation is an important risk factor for invasive fungal infections.[19] As observed in a study, 48% of patients who developed mucormycosis in India had been admitted to the ICU and the majority of them received invasive ventilation.[16]
6. **Poor hygiene and sanitization in hospitals.** Fungal growth in damp buildings is a significant problem. Excess indoor moisture leads to the growth of microorganisms such as molds and fungi. *Penicillium chrysogenum*, *Acremonium*, *Rhizopus*, *Mucor*, and *Aspergillus versicolor* are the most commonly encountered fungal species in water-damaged buildings.[20] There are many hospitals in India with old buildings that have damp walls, increasing the risk of fungal infections.
7. **Excessive use of zinc supplements.** Zinc supplements were used very frequently in the treatment of COVID-19 in India. A study has shown that R. arrhizus isolates grew better with zinc enrichment in vitro, which seems to support the hypothesis that excessive zinc supplementation might have contributed to the pathogenesis of COVID-19-associated mucormycosis.[21]
8. **Oxygen use.** At the peak of the pandemic, there was a shortage of medical-grade oxygen in India, therefore industrial oxygen was used, which was possibly not sterile. Contaminated water used in the humidifier could be another reason for COVID-19-associated mucormycosis. This is just a hypothesis, there is no proven evidence for that to date.

The surge in the number of mucormycosis cases appears to be caused by the intersection of two crises: COVID-19 and poorly controlled diabetes in the setting of the pandemic.

CLINICAL FEATURES

According to a review by Jeong *et al.*, the most common clinical presentations of mucormycosis are rhino-orbital-cerebral (34% of cases), pulmonary (21%), cutaneous (20%), and disseminated infection (14%).[22] In patients with hematological malignancies, the main clinical form of the disease is pulmonary. In India, rhino-orbital-cerebral presentation associated with uncontrolled diabetes mellitus was the predominant clinical presentation, and isolated renal mucormycosis has emerged as a new clinical entity.[23] The most common signs and symptoms of rhino-orbital-cerebral disease include fever, followed by nasal complaints such as blackish discharge from the nose, nasal ulceration or necrosis, periorbital or facial swelling, and ophthalmoplegia (Figure 1). Headache and altered sensorium are more common when the disease infiltrates into the brain. Pulmonary mucormycosis can present as fever, cough, and non-resolving pneumonia usually involving both lungs. Gastrointestinal mucormycosis has non-specif-

FIGURE 1. Rhino-orbital-cerebral mucormycosis

ic clinical presentation, such as dyspepsia and enigmatic diarrhea, and can rarely present as acute peritonitis due to perforation of the gut.

DIAGNOSTIC WORKUP

The diagnosis of mucormycosis is mainly based on histopathology. It can also be confirmed by a positive fungal culture but unfortunately, cultures are seldom positive. Rarely, fungal cultures can even be falsely positive due to the presence of benign mucormycosis-causing fungi in the airways of healthy adults. Therefore, positive cultures should always be correlated with the clinical picture. There is no data regarding the benefits of fungal biomarkers, such as Beta-D-glucan or Galactomannan, in diagnosing mucormycosis. Molecular methods, such as PCR on histopathological samples, are still under investigation, though there are encouraging results from a few recent studies.[24–26] Rhino-orbital-cerebral mucormycosis should be suspected in diabetic patients who have very poor glycemic control or have a history of diabetic ketoacidosis and present with complaints of blackish nasal discharge, proptosis, and ophthalmoplegia, or altered mental sensorium. These patients should undergo an ENT examination with nasal scraping, nasal endoscopy, and histopathology examination of the sample, to look for aseptate hyphae with right-angle branching. The spread of infection to the orbits and the brain can be confirmed by a contrast MRI. The diagnostic workup also includes histopathology and fungal culture from the sputum or bronchoalveolar lavage specimens in case of pulmonary infections, endoscopy and biopsy specimens in case of gastrointestinal infection, and percutaneous kidney biopsy specimens or nephrectomy in case of renal infection.

MANAGEMENT

The treatment of this lethal infection involves a combination of medical and surgical therapies, with early initiation of antifungal drugs and surgical debridement of the affected tissues.[27,28] One of the most important components of treatment is the elimination of all possible risk factors such as acidosis, uncontrolled glycemia, use of immunosuppressive drugs, and neutropenia.

Surgical management

The surgical management of mucormycosis involves the aggressive debridement of the affected tissues, which leads to improved clinical outcomes, especially in rhino-orbital-cerebral infections.[29,30] In some cases, the intervention poses significant challenges because it can lead to a disfigurement of the face due to the removal of vital tissues like the palate, nasal cartilage, and orbit. In case of pulmonary mucormycosis, there is some evidence that early localized infections were cured through lobectomy. However, many patients present extensive pulmonary involvement, and surgery is not possible.

Medical management

Medical management involves the early initiation of antifungal drugs. Amphotericin B is the first-line antifungal therapy of choice, and it is available in three forms: amphotericin B deoxycholate, liposomal amphotericin B, or the amphotericin B lipid complex.[31,32] Due to their better toxicity profile, most physicians prefer liposomal amphotericin B or amphotericin B lipid complex. The initial dose is 5 mg/kg/day, which may be titrated up to 10 mg/kg/day in severe cases.

There are case reports where isolated renal mucormycosis was cured using amphotericin B deoxycholate. The lipid-based preparations are not recommended in renal mucormycosis because they do not penetrate well into the renal tissue. There is no data regarding the effectiveness of combination antifungal therapy. Furthermore, it is not practical to give intravenous injections of amphotericin B for a prolonged period; once the patient becomes stable or is discharged, they can be shifted to oral posaconazole or isavuconazole. Usually, oral posaconazole delayed-release tablets are used. The dose of oral posaconazole is 300 mg every 12 hours on the first day of treatment, and then 300 mg once a day.[33] The target of oral therapy is to achieve trough levels of more than 1 μg/mL after one week of therapy. It is more cumbersome to use isavuconazole due to its complicated loading dose of 200 mg every 8 hours for six doses, followed by 200 mg once daily after 24 hours from the last loading dose. Both oral posaconazole and isavuconazole are tolerated well, with minimal side effects. There is no consensus on the duration of the therapy. In general, most physicians prefer to give antifungals until there is complete resolution of the disease both clinically and radiologically. Usually, antifungals are given for months and rarely lifelong in patients whose immunosuppression cannot be rectified.

PROGNOSIS

In general, the prognosis of mucormycosis is poor, with the rare exception of cutaneous involvement. Risk factors for mortality include disseminated infection, persistent organ failure, and infection with the *Cunninghamella* species. Patients with infection confined to the sinuses have the best prognosis, while mortality from rhino-orbital-cerebral mucormycosis ranges from 25% to 62%.3 In patients with pulmonary mucormycosis, the prognosis is even worse, with mortality rates as high as 87%.

CONCLUSIONS

A combination of uncontrolled diabetes and simultaneous use of corticosteroids is a major risk factor for the surge of mucormycosis in COVID-19 patients. All efforts should be made to keep tight control of glycemia in COVID-19 patients along with judicious use of corticosteroids. The treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy.

CONFLICT OF INTEREST

Nothing to declare.

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Journal of Interdisciplinary Medicine

ORIGINAL RESEARCH AND REVIEW

GENERAL SURGERY // ANATOMY

Stoma-Related Complications: A Single-Center Experience and Literature Review

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Received: March 30, 2022
Accepted: June 20, 2022

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ABSTRACT

Introduction: The creation of an abdominal stoma is a common procedure performed by surgeons as a part of the treatment for benign and malignant conditions in general surgery. Stoma formation is simple, but sometimes the associated postoperative complications have an impact on the patients' physical and psychological state. The majority of complications do not require reoperation, but when it is indicated, we have to assess the most appropriate option for the patient. **Material and Methods:** We conducted a retrospective study in a single surgical center, the Department of Surgery, Mureș County Hospital, Târgu Mureș, Romania, using data from patients who have been admitted under elective conditions for stoma-related complications between 2005 and 2019. **Results:** A total number of 877 ostomies (653 colostomies and 224 ileostomies) were performed, and 157 patients (17.9%) developed some type of stoma complication and required surgical intervention. The mean age was 64.5 ± 2.1 years, with a male-female ratio of 1.3 to 1. The leading comorbidities included cardiovascular disease (52.2% of cases), obesity (22.2%), and diabetes (18.4%). Parastomal hernia was the most frequent complication (47.5% of cases), followed by stoma prolapse (23.4%), parastomal stenosis (20.3%), and parastomal infection (8.2%). There was an association between age and the type of complication: parastomal hernia, stoma prolapse, and stenosis were more frequent in the elderly; parastomal infection was more prevalent in young patients. A longer hospital stay was observed in case of parastomal hernia. **Conclusions:** Stoma formation is associated with significant morbidity. Typically, the complications appear in the elderly. Conservative treatment is essential, but some of the late complications, such as parastomal hernia, stoma stenosis, stoma prolapse, and parastomal infection, require a surgical solution. Parastomal hernias are the most common complications, frequently associated with comorbidities and prolonged hospitalization.

Keywords: stoma, parastomal hernia, stenosis, parastomal infection, prolapse

INTRODUCTION

The term *stoma* comes from Greek terminology and means opening or mouth. It is defined as a natural or artificial communication between the external environment and the cavities of the body. In general surgery, the basic concept is that fecal flow is diverted from the pathological site by bringing the end of the bowel through the anterior abdominal wall.[1] Stoma formation is a widely and commonly performed surgical technique in colorectal surgery, most frequently in malignant diseases, but also in benign ones, such as inflammatory bowel disease or diverticular disease, when no other options are available.[2]

Creating a stoma is usually the final step of an emergency abdominal surgery or of a difficult approach in elective surgery. The most commonly performed stomas are the ileostomy and colostomy. Stomas may be temporary or permanent. Temporary stomas are performed to protect the distal part of the bowel or to relieve bowel obstruction in case of emergency surgery. Permanent stomas are performed in case of incongruency of the distal and proximal part of the bowel, when primary anastomosis creation is unsafe due to inflammation, vascularization, or distal bowel resection.[3]

Based on their spatial distribution, stomas can be categorized into loop or end stomas. A double-barreled or loop ostomy is called external diversion, and when it is performed in a definitive manner, its aim is to relieve bowel obstruction in case of palliative procedures when the tumor is unresectable.[4] Usually, the most appropriate approach is a transverse or sigmoid colostomy.[5] Temporary external diversions are used to protect the distal anastomosis or to solve the bowel obstruction until the blockage or tumor is resected.[6] During the creation of end stomas, the proximal part of the bowel represents the ostomy. The most frequent ostomy is positioned in the left iliac fossa as the last step of the commonly performed Hartmann's procedure.[7]An end ileostomy is more frequently placed in the right iliac fossa as the endpoint of total colectomy or external diversion in case of unresectable extensive colon tumors.[8]

Stoma-related complications

The formation of an ileostomy or colostomy is a lifesaving surgical procedure and is associated with significant morbidity.[9] Careful follow-up in an outpatient clinic is essential to recognize any complications. Stoma-related complications are widely described, and several authors have reported an incidence ranging between 2.9% and 81.1%.[10–12]

A significant proportion of these complications require surgical intervention. It has been demonstrated that the presence of obesity,[13] cardiorespiratory pathology, and emergency surgery may increase the risk of complications.[14] The complications are commonly influenced by the type of stoma and can be avoided by rigorous surgical planning, but postoperative care and patient education are also mandatory. There is a consensus to group these complications according to the elapsed time from the surgical procedure. Commonly, they are registered and broadly classified as early and late complications.

Early complications typically occur within 30 days of surgery, while late complications occur after 30 days. Early complications include inappropriate location, fluid and electrolyte imbalances, peristomal skin complications, stoma ischemia/necrosis, and stoma retraction. Late complications include stomal prolapse, stomal stenosis, peristomal infection/pyoderma gangrenosum, and parastomal hernia.[15,16]

Early complications

Generally, an inadequately placed stoma does not reveal its real degree of morbidity until the patients are discharged and try to restart their daily activities. Stomas placed in unfavorable locations can have consequences such as skin irritation, leakage of effluent and gas, skin breakdown, trauma, and poor visualization of the stoma.[17]

In the preoperative period, patient assessment is necessary to mark the ideal site for the stoma before starting the surgery. During emergency surgery, when this is not possible, the best place for a stoma is at two-thirds of the imaginary line connecting the anterior superior iliac spine and the umbilicus.[18,19]

Dehydration and electrolyte imbalances occur more often in case of ileostomies. There is increased output and compromised fluid absorption due to post-procedural bowel edema. Being a transient state, 49% of high-output stomas are resolved spontaneously and 51% require medical treatment during hospitalization.[20]

Peristomal skin complications, such as irritation and ulcerations, are the consequences of inappropriate stoma care and stoma construction. There is a particularly high risk of peristomal skin complications in obese patients, occurring in 18–55% of cases. Proper management can help to heel the damaged area and to prevent further skin inflammation and stripping.[21]

The impairment of blood supply during stoma formation can lead to ischemia and necrosis, which is more common following colostomy than ileostomy. The incidence of compromised vascularization has been reported to range from 2.3% to 17%.[22] The leading causes of insufficient blood supply are high ligation, vascular damage, and tight

abdominal window. Early recognition of stomal ischemia is mandatory because poor vascular supply could lead to delayed complications.

Stoma retraction is caused by excess tension on the diverted bowel loop, which is typically the consequence of inadequate mobilization. It is important to conduct a careful assessment for this complication and also to take into consideration a minimally invasive intervention before stoma revision or resection by laparotomy.[23]

Late complications

Parastomal hernia

A parastomal hernia is an incisional hernia associated with an abdominal wall stoma. The incidence of parastomal hernias varies a lot and it is correlated with the type of stoma and the accuracy of follow-up.[24] They occur more frequently in case of colostomies, and the clinical presentation includes pain, skin modification, leakage, and the appearance of a lump near the stoma, with a high risk of bowel obstruction. Stoma-related hernias can occur in up to 40% of stomas, and the leading cause is an excessively large fascial opening.[14,25,26] Surgical repair is essential with either a sutured technique or prosthetic mesh. Nowadays, there is also a recommendation to use a prophylactic mesh during the surgical preparation of stomas.[27,28]

Stoma prolapse

Stoma prolapse is a full-thickness protrusion of the bowel through the stoma due to the excessive length of the bowel loop or a wide fascial opening. Its incidence is estimated between 2% and 26%.[29] This complication can be treated conservatively with gentle manual pressure or with osmotic therapy (ex. table sugar) in case of edema.[30,31] Surgical revision and resection are performed when the prolapse is irreducible, ulcerated, or recurrent.[32] A novel and simple technique with low recurrence includes surgical stapling with excision of the prolapsed bowel segment.[33,34]

Stoma stenosis

Stoma stenosis is a late complication that the patient may experience after a period that can vary from a few weeks to years, and its incidence has been reported at 2% to 14%.[10,35,36] Local ischemia is the usual underlying factor, but infection or retraction of the stoma may also lead to stenosis. First-line treatment includes dilation or irrigation, but pressure could cause damage which will heal with fibrosis and further stenosis. The definitive solution is surgical treatment by external stoma revision and recreation, or by laparotomy.[29]

Peristomal infection/abscess/pyoderma gangrenosum

Infectious complications, such as abscess formation, are usually uncommon in the early postoperative period. Peristomal abscesses usually require surgical intervention such as incision and drainage. Surgeons must be aware of the risk of fistula formation after a surgically solved peristomal abscess.[22] Pyoderma gangrenosum is an ulcerated area with a painful, well-defined, erythematous zone observed firstly by the patient and frequently during stoma pouch application.[37] This skin lesion is associated more often with inflammatory bowel disease, with an incidence of 0.6% of the total stoma cases.[16] Conservative treatment with systemic corticosteroids, topical steroids, and antibiotics is included in the initial treatment; surgical intervention and negative pressure wound therapy may be necessary in case of extended lesions.[38,39]

Late complications require monitorization by specialists, such as a dedicated nurse, surgeon etc., both for prevention and early intervention. Maintaining the stoma in optimal conditions leads to a better quality of life for the patient and lower financial costs.[40]

The aim of this study was to conduct a short review of the literature and to present the experience of a single general surgery center in regards to stoma-related early and late complications.

MATERIALS AND METHODS

A retrospective observational study was conducted during a 15-year period in the Department of Surgery, Mureș County Clinical Hospital, Târgu Mureș, Romania, using data from patients who have been treated surgically for stoma complications.

A total number of 877 stomas, both ileostomies and colostomies, were created between January 2005 and December 2019 in our department. Patients who required only conservative treatment were excluded from the study. All patients included in the study have been treated with an open surgical approach. Patients with incomplete clinical data were also excluded.

The collected data included the patients' age, gender, length of hospital stay, body mass index (BMI), and main comorbidities such as cardiovascular disease, diabetes mellitus, and obesity.

We grouped the patients according to the main diagnosis on admission into four main categories: parastomal hernia, stoma stenosis, stoma prolapse, and parastomal infection/pyoderma gangrenosum. We analyzed the surgical procedure protocols to assess the most important steps. From the electronic database and clinical files, the post-

TABLE 1. Clavien-Dindo postoperative complication scale (Dindo et al., 2004)

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
IVa	Single-organ dysfunction (including dialysis)
IVb	Multi-organ dysfunction
V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC – intermediate care; ICU – Intensive care unit

operative complications were classified according to the Clavien-Dindo classification system and grouped into five categories (Table 1).[41,42]

Statistical analysis

Descriptive and inferential statistics were performed. The normality of the distribution of continuous variables was tested with the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or as median (25th percentile, 75th percentile) and compared using one-way ANOVA or the Kruskal-Wallis test. Categorical variables were displayed as frequencies, n (%), and between-group comparisons were performed by using the Chi-square test. A value of $p < 0.05$ was considered significant. The IBM SPSS Statistics 22 (IBM Corporation, USA) software was used for the statistical analysis of the data.

This study is part of the project "Studiul factorilor de risc și a complicațiilor în chirurgia cancerului colorectal (Study of risk factors and complications in colorectal cancer surgery)" and was approved by the Ethics Committee for Scientific Research of the "George Emil Palade" University of Medicine Pharmacy, Science and Technology of Târgu Mureș, Romania.

RESULTS

During the 15 years, a total number of 877 ostomies have been performed (653 colostomies and 224 ileostomies). The number of patients who were admitted for stoma-related complications that required surgery was 157 (17.9% of the total ostomies). The mean age of the studied population was 64.5 ± 2.1 years, and the male-female ratio was 1.3

TABLE 2. Obesity incidence and degree of obesity in the study population

Obesity	BMI	N	%
Normal	19–24.9	61	38.6
Overweight	25–29.9	61	38.6
Obesity I	30–34.9	28	17.7
Obesity II	35–39.9	3	1.9
Obesity III	>40	4	2.5

TABLE 3. Anesthesia type during surgical interventions

Anesthesia type	N	%
General anesthesia	71	45.2
Spinal	54	34.4
Local	19	12.1
Analgosedation	13	8.3

TABLE 4. Types of stoma complications on admission

Complication	N	%	% of total stoma
Parastomal hernia	75	47.5	8.55
Stoma prolapse	37	23.4	4.21
Parastomal stenosis	32	20.3	3.64
Parastomal infections	13	8.2	1.48

TABLE 5. Comorbidities and mortality rates according to the type of stoma-related complication

	Parastomal hernia	Stoma prolapse	Parastomal stenosis	Parastomal infection
Cardiac pathology, n (%)	34 (45.3)	22 (59.5)	25 (78.1)	1 (7.7)
Diabetes, n (%)	13 (17.3)	7 (18.9)	No data	3 (23.1)
Death, n (%)	6 (8.0)	1 (2.7)	0 (0)	0 (0)
Parastomal infections	13	8.2	1.48	

to 1. Regarding the patients' comorbidities, cardiovascular disease was present in 52.2% and diabetes in 18.4%. Obesity was observed in 22.29% of the population (Table 2).

Surgery was performed in nearly half of the cases (45.2%) under orotracheal intubation and general anesthesia, in slightly more than one-third (34.4%) under spinal anesthesia, and in the remaining patients under local anesthesia or analgosedation (Table 3).

The length of stay (LOS) in the hospital was 9.2 ± 5.4 days, ranging from a minimum of 1 day to a maximum of 36 days. The overall stoma complications-related mortality rate was 4.5% (n = 7).

The most common complication was parastomal hernia, which occurred in nearly half of the cases. Stoma prolapse and parastomal stenosis were also frequent. The rarest surgical complications were related to parastomal infections (Table 4).

Cardiovascular comorbidities were the most frequently reported in all types of stoma-related complications, and the highest mortality rate was reported in patients that had presented with parastomal hernia (Table 5).

There was an association between age and the type of stoma complication: parastomal stenosis, stoma prolapse, and parastomal hernia were associated with older age, while patients with parastomal infection were significantly younger. We also observed an association between the BMI and the type of surgical complication, the BMI of patients with parastomal hernias being significantly higher compared to subjects with other types of stoma complications. The longest LOS was registered in patients with parastomal hernias, and the lowest was observed in subjects admitted for parastomal stenosis (Table 6).

Regarding the grade of surgical complications, low-grade complications (Clavien-Dindo I and II) were observed in most of the cases (87.4%). The distribution of postoperative complications according to the Clavien-Dindo classification are summarized in Figure 1.

An association was observed between the type of surgical complication and the Clavien-Dindo grade of complication ($p < 0.001$). Clavien-Dindo class V was most frequently encountered in patients with parastomal hernias (8%), and the most common risk category across all types of stoma-related complications was Clavien-Dindo class I (Table 7).

DISCUSSION

Stoma formation is a common procedure in general surgery, and its potential morbidity occurs during its creation and in the postoperative period. Complications appear quite frequently, but most of them can be treated using conservative methods; only 15–20% of patients require reoperation.[22,43] In our case study, 17.9% of stoma patients required readmission and surgery for stoma-related complications. This percentage may vary in time due to the lack of out-patient clinics and poor follow-up of these patients in Romania. High incidences of stoma complications have been reported mainly in emergency surgery, but they also appear in elective conditions. The number of cases could also vary according to the type of hospital in which these evaluations are conducted (emergency versus non-emergency hospitals). All of our patients have been admitted by elective conditions.

TABLE 6. Gender, age, BMI, and LOS according to the type of stoma-related complication

	Parastomal hernia	Stoma prolapse	Parastomal stenosis	Parastomal infection	p value
Sex, male/female, n (%)	44 (58.7)/31 (41.3)	23 (62.2)/14 (37.8)	15 (46.9)/17 (53.1)	7 (53.8)/6 (46.2)	0.452
Age (years)	64 (57.5–73.5)	67 (57.5–72)	67.5 (57.5–72)	54 (47–70)	0.04
BMI (kg/m^2)	27.7 ± 4.5	24.7 ± 3.5	26.4 ± 5.9	25.6 ± 6.0	0.01
LOS (days)	10 (7.5–13.5)	7 (4–12)	4.5 (3–8)	9 (7–16)	< 0.001

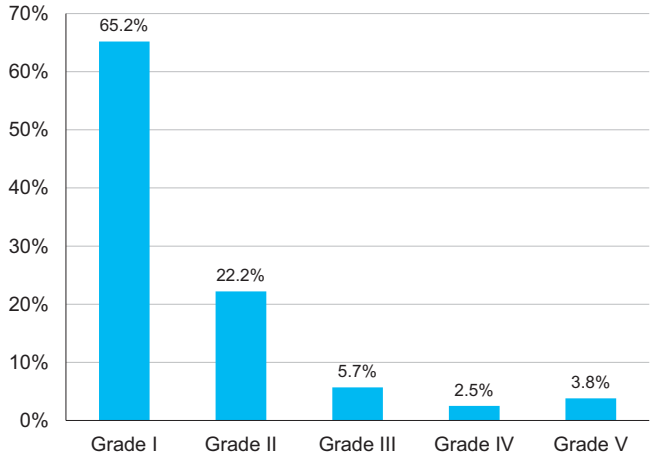

FIGURE 1. Distribution of complications according to the Clavien-Dindo classification

Obesity has been proven to influence the clinical evolution of patients who require stoma formation. Creating a stoma in obese patients remains a problem and requires more attention from the patient, the stoma care nurse, and the surgeon in order to avoid potential complications.[44] Patients with a BMI ≥25 kg/m^2 are at a significant risk to develop parastomal hernias.[45] In our experience, obesity was present in 22.29% of cases, and the most frequent complication was parastomal hernia.

A review reported by Zelga *et al.* found that age over 65 years, female sex, BMI higher than 25 kg/m^2, diabetes mellitus, abdominal malignancy, and lack of perioperative stoma site marking are risk factors associated with increased likelihood of stoma-related complications.[46] Our results showed a mean age of 64.5 years and the presence of diabetes in 18.4% of cases.

Sometimes the surgical procedure to solve these complications requires a median or parastomal laparotomy, for which proper muscular relaxation is indispensable during anesthesia. According to a study on parastomal prolapse by Makoto *et al.*, either general or spinal anesthesia was considered necessary.[32] In our study, the preferred type of anesthesia in nearly 80% of the cases was general or spinal.

Parastomal hernia has been reported as the most common complication in patients with permanent stoma,[47] occurring in more than 30% of the patients.[48] A Korean study, based on a single surgeon's experience, reported an incidence of 6.6% for stoma complications.[49] In our experience, parastomal hernia was the most frequent complication, with an overall incidence of 8.55%, which represented 47.5% of the total number of complications.

The duration of hospital stay was also analyzed for all patients. Several studies reported a length of hospital stay ranging between 5.1 and 10.5 days after parastomal hernia repair.[50–52] Our data was similar, with a median LOS of 10 days, and in the case of parastomal hernia surgery, the LOS was higher.

Regarding the postoperative result of stoma complication treatment, most of the cases (87.4%) required non-surgical intervention (Clavien-Dindo I and II), and only a few patients had a major complication with surgical reintervention.

CONCLUSIONS

Stoma formation is a common surgical procedure with significant morbidity. The key point of this treatment is to summarize the comorbidities in the preoperative period and to recognize post-operative complications early. Typically, complication rates are higher in the elderly, but fortunately, most of them can be treated conservatively. When the surgical approach is discussed, the surgeon must be aware of the presence of comorbidities such as obesity, cardiovascular pathology, and diabetes. Most of the late complications, such as parastomal hernia, stoma stenosis, stoma prolapse, and parastomal infection, require surgical management. Parastomal hernias are the most common complications, which are frequently associated with comorbidities and prolonged hospitalization periods.

CONFLICT OF INTEREST

Nothing to declare.

TABLE 7. The association between stoma complication type and Clavien-Dindo grade

Complication type, n (%)	CLAVIEN-DINDO classification				
	I	II	III	IV	V
Parastomal hernia	35 (46.7)	24 (32.0)	7 (9.3)	3 (4.0)	6 (8.0)
Parastomal infections	9 (69.2)	2 (15.4)	2 (15.4)	0 (0)	0 (0)
Stoma prolapse	32 (86.5)	4 (10.8)	0 (0)	1 (2.7)	0 (0)
Parastomal stenosis	27 (84.4)	5 (15.6)	0 (0)	0 (0)	0 (0)

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ORIGINAL RESEARCH

DENTAL MEDICINE // TECHNOLOGY OF DENTAL MATERIALS

In Vitro Study of Mechanical Properties of Teeth Restored with Bulk-fill and Universal Composites Using Different Dentin Adhesives

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ARTICLE HISTORY

Received: June 15, 2022
Accepted: June 29, 2022

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ABSTRACT

Background: The most common dental materials are resin composite direct restorative materials and dentin adhesives, which are marketed with different techniques, application recommendations, and compositions, making it difficult to choose the most suitable material and method for different cases. The present study **aimed** to investigate mechanical properties of teeth restored with universal and bulk-fill composites, by using different dentin adhesives and techniques, under in vitro conditions. **Material and methods:** The study was carried out on freshly extracted premolar and molar teeth. After cavity preparation, the teeth were restored with conventional and bulk-fill resin composites, using different adhesive techniques. To assess the effect of the cavity preparation, the direct restoration, and the adhesive protocol on the tooth structure, a transillumination method and Vickers' microhardness measurements were carried out. **Results:** The universal composite showed an average hardness of 55.35 HV at the occlusal level of the restoration, while the bulk-fill composite showed an average of 79.93 HV at the same level. A statistically significant difference was found between the hardness values of the two composites ($p = 0.02$). The transillumination test revealed micro-fissures in the tooth structure in the first phase after cavity preparation and also after polymerization. **Conclusions:** The bulk-fill composite showed higher hardness values than the universal composite. The tested dentin adhesives did not significantly affect the hardness of the dentin at the level of the adhesive interface. Fissures can appear in any phase of the direct restoration, after cavity preparation and polymerization.

Keywords: resin composite, microhardness, dental tissue, mechanical properties, bulk-fill composite

INTRODUCTION

Thorough knowledge of the morphology and histology of teeth and periodontium is essential for an appropriate conservative treatment. Dental caries occur through a process of progressive deterioration of the hard tissues of the tooth. After removal of the carious lesion, the final step in the treatment of caries with conservative rehabilitation of the tooth includes direct tooth restoration.

The history of resin composites as direct esthetic restorative materials began around the 1960s, when Bowen invented the Bis-GMA matrix, mixed with silicate filler. Since then, resin composites have gone through many modifications and improvements, resulting in improved mechanical properties, esthetics, and durability.[1] Their popularity is evidenced by the fact that more than 500 million direct dental restorations are placed around the world each year.[2] However, despite its many advantages, clinicians are still not entirely satisfied resin composites. Therefore, newer types of resin-based materials were introduced in order to reduce the drawbacks encountered in clinical practice.

Universal resin composites are used in 2 mm thick layers, which present a high potential for failure in the lateral areas. A new type of resin, the bulk-fill composite was therefore developed, which can be used in a single increment of 4–5 mm, usually in the lateral areas. Adequate retention must also be ensured when using these materials. Thus, various acids and bonding agents are essential components of resin composite systems. After the complete removal of caries, the next step of the conservative treatment includes acid etching, which produces microretentions on the surface of the dental hard tissues. This is followed by the application of dental adhesives, which create an inseparable mechanical bond between the enamel/dentin and the resin composite. Due to the key role of adhesives, a large number of potential defects can occur during their use, which can impair or make it impossible to achieve an adequate restoration. The type of adhesive and the technique used to create strong bonding between the dental hard tissues and the restorative material, as well as the type of the resin composite have an important impact on future dental restorations. Three basic types of adhesive protocols can be used: total-etch (when enamel and dentin are etched with 37% orthophosphoric acid before applying the bonding agent), selective-etch (when only the enamel is etched before applying the bonding agent), and self-etch (when no etching step is needed, a self-etch type bonding agent is used). The microhardness of the tooth structure may be altered and fissures might appear during these processes.

The present study aimed to investigate the appearance of new fissures in the dental hard tissues and the microhardness level of the restoration, in teeth restored with bulk-fill and universal composites, by using different dentin bonding agents and techniques, under in vitro conditions.

MATERIALS AND METHODS

The study was carried out on freshly extracted premolar and molar teeth. The teeth were removed due to orthodontic and periodontal reasons. To study the appearance of fissures, a transillumination method was used. In the first phase, photographs were taken of the intact teeth using a DSLR camera (Nikon D3100) and a macro lens (Tamron 90 mm) with a magnification ratio of 1:1 and a standardized LED light source. A total of four photographs were taken of each tooth, corresponding to the four surfaces: mesial, distal, buccal, and lingual. The photographs revealed enamel fissures and defects suffered during extraction (Figure 1).

After documentation, mesio-occluso-distal cavities were created. The cavities were standardized, 4 mm deep and 2 mm wide in the bucco-lingual direction. The depth of 4 mm was determined according to the tip of the highest cusp of the tooth so that the actual depth of the cavity varied between 1.5 and 3.5 mm. Standard dimensions were set using a caliper and a periodontal probe.

TABLE 1. The resin composites, adhesives, and techniques used in the different sample groups

Group name	Restoration material used	Adhesive used	Adhesive technique used
Group 1	Filtek™ Bulk-Fill (3M ESPE)	Adper™ Single Bond (3M ESPE)	Total-etch
Group 2	Filtek™ Bulk-Fill (3M ESPE)	Optibond™ Universal (Kerr)	Self-etch
Group 3	Filtek™ Bulk-Fill (3M ESPE)	Optibond™ Universal (Kerr)	Selective-etch
Group 4	Filtek™ Bulk-Fill (3M ESPE)	Gluma Bond Universal (Kulzer)	Self-etch
Group 5	Filtek™ Bulk-Fill (3M ESPE)	Gluma Bond Universal (Kulzer)	Selective-etch
Group 6	Charisma® Classic (Kulzer)	Optibond™ Universal (Kerr)	Self-etch

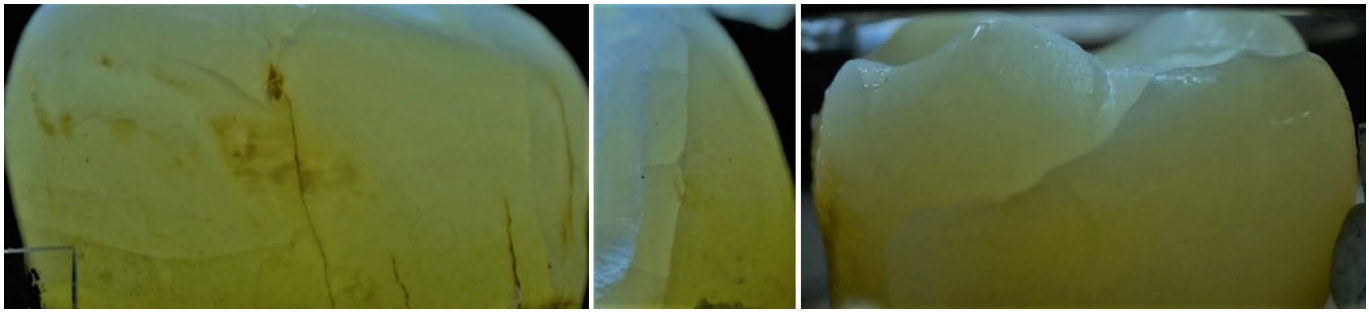

FIGURE 1. Fissures revealed on different tooth surfaces on photographs taken with the transillumination method

Photographs using the transillumination method were taken again of the prepared teeth, followed by grouping of the teeth according to different dental materials and restoration techniques. We defined a total of six groups, with four molars/premolars in each group. Following the manufacturer's instructions, we used three types of dentin adhesives combined with two different resin composites, as seen in Table 1.

The teeth with fillings were incubated at 37°C in a physiological solution, and photographs were taken using the transillumination method again after 24 hours. All the photographs were assessed qualitatively by two trained operators.

The following step was to place the teeth in a standardized mold made of condensation silicone (Zetaplus, Zhermack) and cast with dental stone (Fujirock Premium, GC). The incubated teeth were sectioned on the middle line in the mesio-distal direction using a low-speed precision cut-off machine (Micracut 151).

Microhardness was measured on the sectioned surfaces using a Vickers Hardness Tester CV-AAT 400. The measurements started each time from the occlusal surface of the resin and progressed gradually toward the dentin adhesive interface (DAI). The first four measurements were performed in the resin composite (occlusal surface, at 0.5 mm, at 1 mm, and at 1.5 mm in the composite), the fifth measurement reached the DAI each time, and the last measurement was performed in the dentin, at 0.5 mm from the DAI. During microhardness testing, we made a pyramidal indentation on the specimens, using a diamond-shaped indenter to apply a load of 50 gf (corresponding to a force of 0.490 N) for 15 s. We measured the diagonals of the indentations using a calibrated optical microscope and evaluated the hardness as the mean stress applied underneath the indenter (Figure 2).

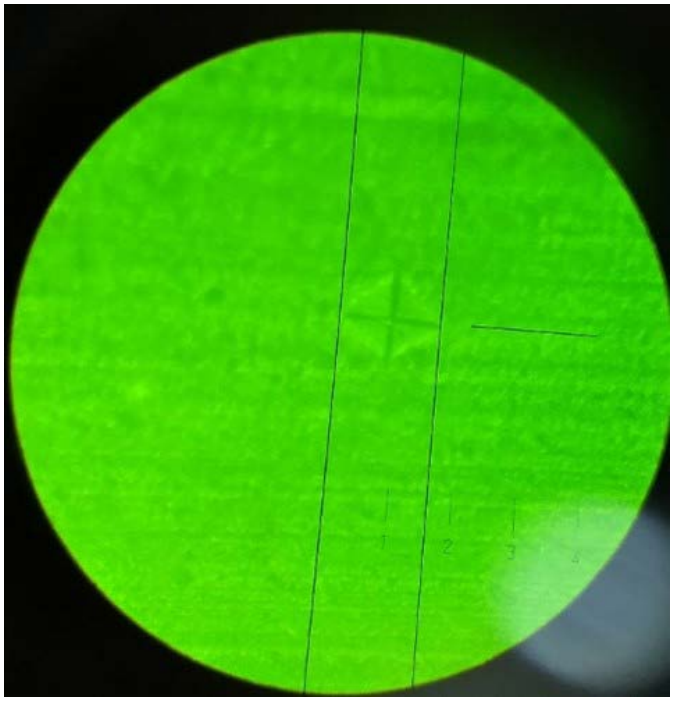

FIGURE 2. Indentation on the surface, observed under the microscope

Statistical analysis

The obtained values were introduced into Microsoft Excel tables, and non-parametric Kruskal-Wallis and Mann-Whitney tests were performed. Pearson's correlation coefficient was calculated using GraphPad Prism software, using a statistically significant threshold of $p < 0.05$.

RESULTS

A total of 144 measurements were performed at different levels of the composite restoration and dentin in the six sample groups (Figure 3).

We found no significant difference between the hardness values measured at the occlusal surface and at a depth of 1.5 mm in the bulk-fill restoration samples ($p > 0.05$). The hardness of the universal composite restoration samples from Group 6 showed significantly lower values at the composite levels compared to the bulk-fill restoration samples ($p = 0.02$) (Figure 4); no significant differences were detected at the dentin level ($p > 0.05$).

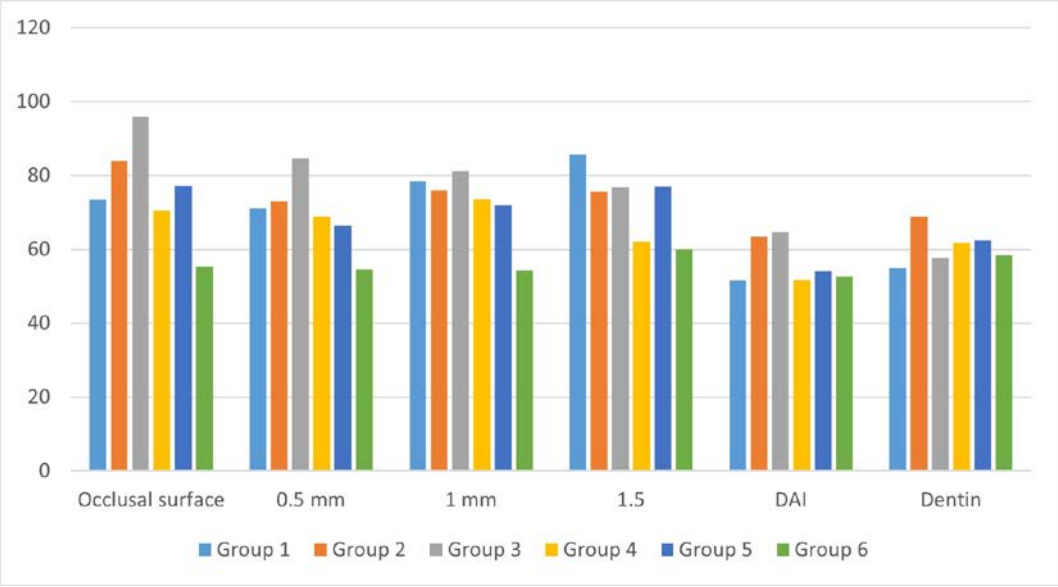

FIGURE 3. Vickers microhardness measurements at different depths

The microhardness values of the dentin levels of different groups restored with bulk-fill composite were compared according to the adhesive protocol used. Selective-etch and self-etch techniques did not show significant differences ($p = 0.475$) in regards to microhardness. The lowest dentin tissue hardness (54.98 HV) was measured in Group 1, where a total-etch technique was used, but this was not significantly lower than in the other groups ($p = 0.149$) (Figure 5). The highest microhardness values (68.88 HV) were obtained in Group 3, where a self-etch protocol was applied by using Optibond™ adhesive material.

At the DAI level, no significant differences were found between groups with different adhesive protocols ($p > 0.05$). The lowest microhardness values (51.63 HV) for the DAI level were found in Group 1.

A positive correlation between the microhardness of the occlusal surface composite level and that of the DAI was detected ($R = 0.56$) in the bulk-fill restored groups. In all cases, the microhardness of the composite layers was higher compared to that of the dentin layers, regardless of the adhesive protocol (Figure 5).

The photographs taken using the transillumination method revealed that the majority of new fissures appeared after cavity preparation. The qualitative analysis of

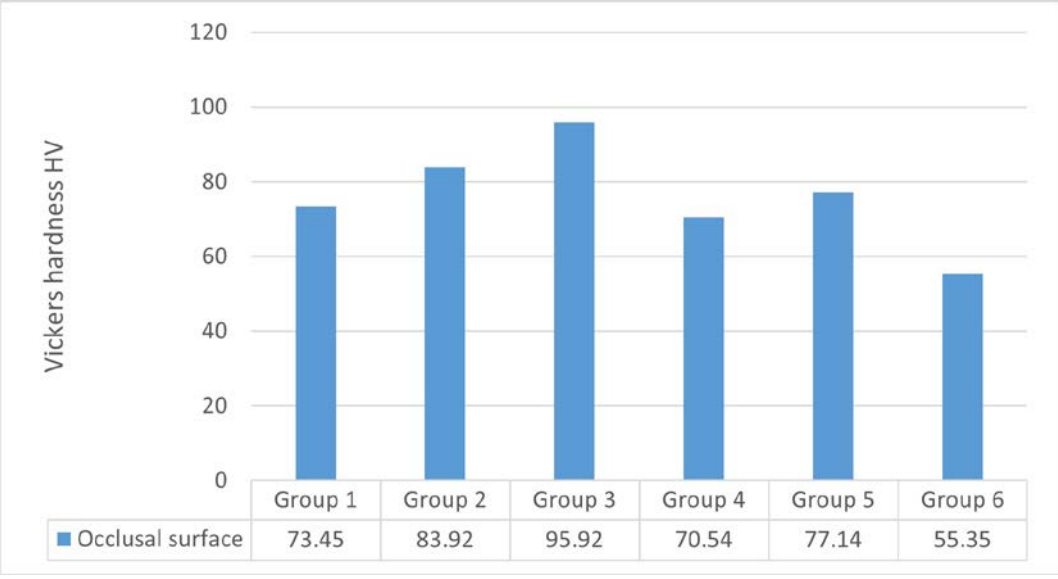

FIGURE 4. Column graph of mean microhardness values measured at the occlusal surface

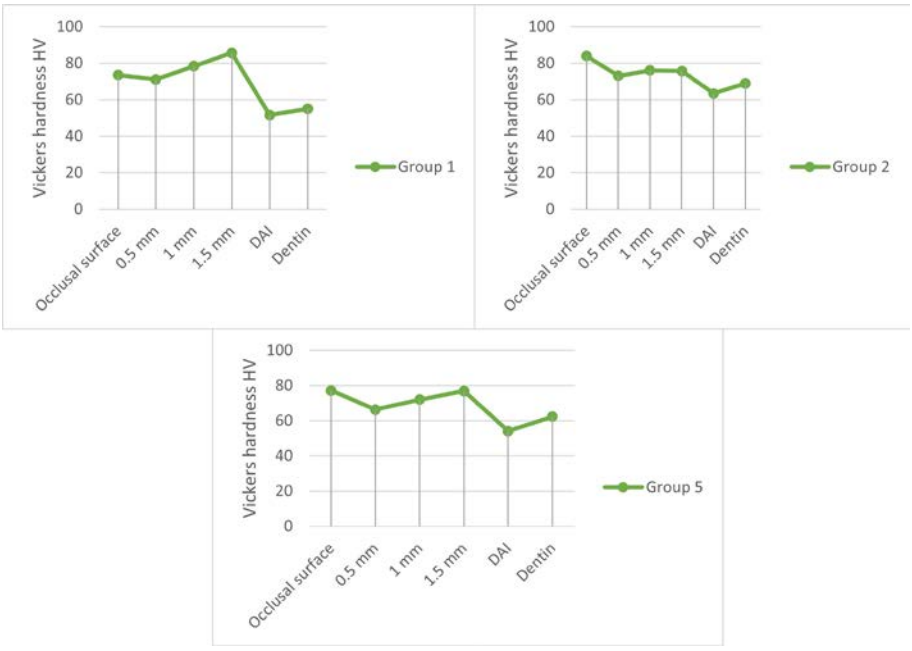

FIGURE 5. Microhardness values at the different measurement levels for three groups with different etching protocols

the photographs made after restoration showed that most fissures appeared in Group 1, where a total-etch adhesive protocol and bulk-fill resin composite were used.

DISCUSSION

Resin composite materials with high values of hardness are recommended for use in the enamel level of teeth. The microhardness of the bulk-fill resin composite material showed higher values compared to the universal composite material. Other studies using bulk-fill resin composites have found no significant differences in resistance compared to universal composites.[3] In case of low-viscosity bulk-fill composites, several studies found lower hardness values compared to high-viscosity bulk-fill composites and universal composites.[2,4] These results might be explained by the fact that low-viscosity materials have a lower filler particle content than high-viscosity resin composites.

Several studies have investigated different bulk-fill type resin composites, since their simple application method shortens chair time. Different bulk-fill materials presented different microhardness values. Comba *et al.* reported that low-viscosity bulk-fill resins showed adequate resistance even at a depth of 4 mm, while high-viscosity bulk-fill composites showed a gradually decreasing hardness after a depth of 2 mm.[5] However, in the present study, measurements were only taken at a depth of 1.5 mm in the composite level, and no significant difference in microhardness was found between different layers.

Another study, also investigating bulk-fill resins, compared the mechanical properties of the materials using different layering techniques. One technique involved inserting the material into the cavity in a single increment (4 mm depth), while the other one involved inserting the material in two 2-mm thick layers. The authors observed decreased microhardness values for in case of the single-layer insertion technique, but this was statistically significant for only one material.[6]

Rooz and Jordehi revealed similar results to ours. They also measured microhardness, using 2 and 4 mm thicknesses of bulk-fill type materials, but they took into consideration the different color shades as a possible influencing factor. They only measured the superficial and the bottom layer of the samples. In their results, the samples with 4 mm thickness showed lower hardness values than the samples with 2 mm thickness.[7]

In studies comparing conventional composites with bulk-fill type composites, it was found that although microhardness was decreased towards the deeper layers of the composite, better resistance and hardness can be achieved with bulk-fill composites compared to conventional composites, especially at cavity depths of 4 mm.[8–11] Lempel *et al.* studied the curing depth of different bulk-fill composites and conventional composites. Another study tested the Bulk Fill Posterior (3M ESPE Filtek) composite

and found no significant differences between the top layer and the deeper layers regarding microhardness.[9]

Most adhesive systems can be used with either total-etch or self-etch techniques. Manufacturers have focused on developing the simplest possible adhesive technology to meet the needs of clinicians for a simple, fast, user-friendly, and technique-insensitive bonding system. Results from previous research have suggested a strong relationship between the bonding agent and the used technique, with some materials performing better with total-etch techniques and others being more sensitive to self-etch techniques.[12] Based on a study published in 2020, a significant difference in bond strength was found as a function of the adhesive and technique used, and the authors recommend the use of acid etching before the application of universal adhesives.[13] However, acid etching might influence the hardness of the dental tissue. Hence, different etching materials and procedures are tested,[14] and different solutions to recover the original microhardness of dentin are studied.[15] In the present study, no significant differences were found between the microhardness of the dentin at the adhesive interface level in the case of different adhesive protocols, but the lowest microhardness values were found when the total-etch technique was used. The acid etching of the dentin resulted in lower microhardness values at the adhesive interface and dentinal levels, but these values were not significantly lower than in other groups. We obtained the highest microhardness values using Optibond™ adhesive with the selective-etch protocol, where the surface of the dentin was not additionally etched. Transillumination was carried out according to the method of Rosatto *et al.*,[2] and similarly to their results, we detected new fissures after cavity preparation and restorations.

CONCLUSIONS

The used dentin adhesives and adhesive protocols did not significantly affect the hardness values of the dentin tissue at the adhesive interface level, although the lowest microhardness values were found in the case of the total-etch technique. The bulk-fill type composite used in the present study showed higher microhardness values than the universal composite. New microfissures appear in the dental hard tissues after both cavity preparation and polymerization of the resin composite restoration.

CONFLICT OF INTEREST

Nothing to declare.

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CASE REPORT

INFECTIOUS DISEASES // IMMUNOLOGY

A Case of Eosinophilic Colitis after BNT162b2 mRNA COVID-19 Vaccination

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ARTICLE HISTORY

Received: May 21, 2022
Accepted: June 28, 2022

ABSTRACT

Background: BNT162b2 is a widely used mRNA COVID-19 vaccine for which 8.2% of participants above the age of 56 years have reported diarrhea as an adverse event. This case report highlights the possibility of eosinophilic colitis in post-vaccination diarrhea. **Case report:** A 72-year-old male patient presented with generalized colicky abdominal pain and acute diarrhea after receiving the first dose of the BNT162b2 vaccine. Laboratory examination revealed peripheral blood eosinophilia with cecal and ascending colon mucosal eosinophilia with 100–130 cells/HPF and eosinophilic cryptitis. The patient's symptoms and eosinophilia resolved spontaneously and did not recur after the second dose of vaccination. More research is needed to confirm eosinophilic colitis as a possible vaccine adverse reaction.

Keywords: COVID-19 vaccine, eosinophilic colitis, vaccine adverse reactions

INTRODUCTION

Vaccines are considered the most promising approach in managing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and are being vigorously pursued.[1] One widely utilized vaccine is the BNT162b2 mRNA COVID-19 vaccine, for which diarrhea was listed as one of the adverse events in 8.2% of participants older than 56 years.[2]

CASE REPORT

We present the case of a 72-year-old Chinese male patient with underlying hypertension, atrial fibrillation with cerebrovascular stroke, and post-stroke seizures who presented with generalized colicky abdominal pain and acute diarrhea after receiving the first dose of the BNT162b2 vaccine. The diarrhea (Bristol Stool Form Scale type 6-7), occurring 4–5 times a day, started 6 hours after receiving the first vaccine dose and lasted for eight days. The patient reported no per rectal bleeding or mucus, and the diarrhea did not improve with self-administered loperamide. He denied any allergy history or other symptoms. His past medications

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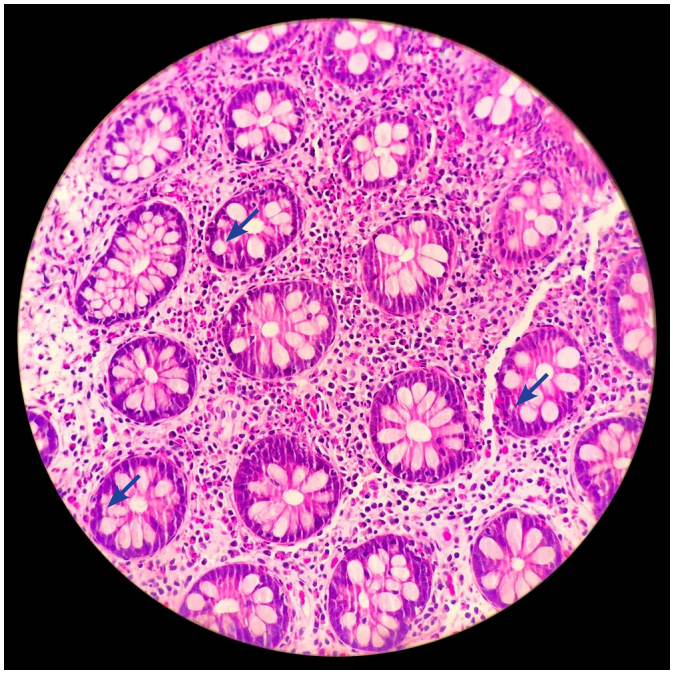

FIGURE 1. Eosinophilic cryptitis (pointed with the blue arrows)

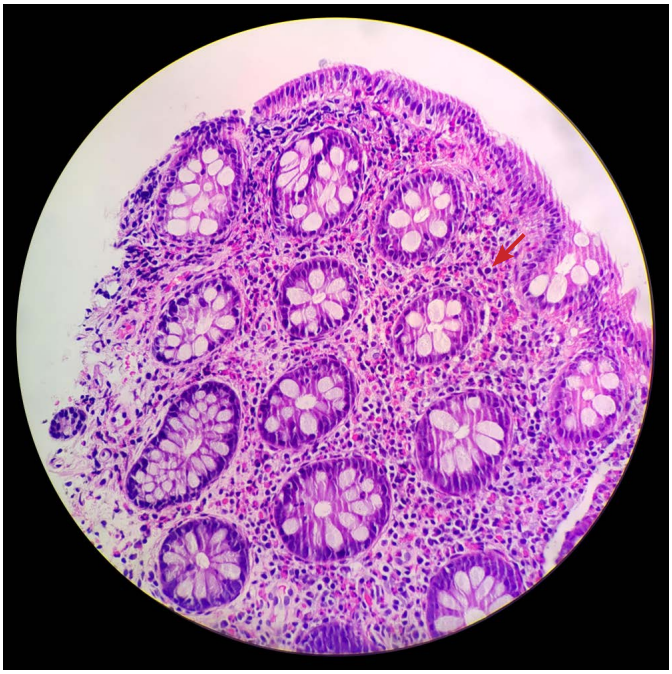

FIGURE 2. Abundant eosinophils in lamina propria (pointed with the red arrow)

included perindopril 4 mg once daily, dabigatran 150 mg twice daily, atorvastatin 40 mg nocte, and levatiracetam 500 mg twice daily. His mother was diagnosed with colon cancer at the age of 75. Other aspects of clinical history and physical examination were unremarkable.

The complete blood count showed isolated peripheral eosinophilia with an absolute eosinophil count of 6.84 × 103/μL (normal range: 0.02–0.5 × 103/μL). Other blood parameters (renal profile, liver function test, thyroid function test, C-reactive protein, and erythrocyte sedimentation rate) were within normal range. Stool bacterial culture and microscopic parasitology examination were negative for pathogens.

In view of his advanced age, no previous endoscopic colorectal cancer screening, and family history of colonic malignancy, a decision was made to perform esophagogastroduodenoscopy (EGD) and colonoscopy on day 7 from symptom onset. The EGD showed antral erythematous gastritis with negative rapid urease test, whereas colonoscopy revealed a histologically confirmed Paris classification 0-Is, Narrow Band Imaging International Colorectal Endoscopic (NICE) Type 1 sigmoid hyperplastic polyp measuring 0.3 cm, which was completely resected by cold snaring. The rest of the colonoscopy examination revealed a normal aspect from the rectum to the terminal ileum. Histopathological examination of random segmental colonic biopsies from the cecum and ascending colon showed mucosal lymphoplasmacytic cell infiltration with increased eosinophil count of 100–130 cells/high power field (HPF) associated with occasional eosinophilic cryptitis (Figure 1 and Figure 2). No eosinophilic crypt abscesses, granulomas, or infective organisms were seen. Other colonic segments and the terminal ileum were histologically normal.

The patient's symptoms resolved spontaneously eight days after the first dose vaccination without any treatment. He received the second dose of BNT162b2 vaccine 21 days after the first dose without reporting any symptomatic adverse reaction. His absolute eosinophil count has subsequently normalized after 34 days from the first dose of vaccination.

DISCUSSION

Diarrhea as a post-vaccination adverse event was not reported in the initial clinical trial. There were also no reports on eosinophilia or eosinophilic colitis (EC) post-vaccination.2 However, diarrhea was reported as an adverse event in 8.2% of patients receiving the BNT162b2 vaccine outside of clinical trials.[2]

Peripheral eosinophil counts are usually elevated in patients with EC but might be normal in approximately 20% of patients.[3] The percentage of peripheral eosinophils among leucocytes can range from 5% to 35%, with an average peripheral blood eosinophil count of 1,000/μL.[4] Allergy is one of the proposed mechanisms of pathogenesis in EC, which could be possible in this patient.[3,5,6]

Eosinophils can be present in normal physiologic states throughout the gastrointestinal tract. The diagnosis of mucosal EC is established by the presence of a higher number of eosinophils than expected on microscopic examination of biopsies of the gastrointestinal tract.[3,7–9] As there is no defined cut-off value for the number of eosinophils per HPF to diagnose EC, the diagnosis should be confirmed by an experienced gastrointestinal histopathologist to assess if the eosinophil count is greater than expected for a particular area. The suggested normal upper limit of eosinophil count for the right colon is 100 per HPF.[10]

CONCLUSIONS

We are reporting a case of EC, with post-BNT162b2 vaccination as a putative cause. The symptoms were self-limiting, and no specific treatment was required. The patient did not develop recurrence or worsening of symptoms after the second dose of vaccination. This novel vaccine utilizes a mechanism of action not previously seen in other vaccines, and as such, more data and research is needed to confirm EC as a possible adverse reaction. Clinicians should be vigilant about the possibility of EC in the event of post-vaccination diarrhea and report it accordingly.

CONFLICT OF INTEREST

Nothing to declare.

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