



Dysphagia-related mucositis in children undergoing chemotherapy: The COMEDY pattern

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Abstract

Objectives: Children undergoing chemotherapy can experience dysphagia due to non-erosive reflux disease (NERD). Oral mucositis (OM) associated with NERD-dysphagia in children with cancer has recently been defined with the acronym COMEDY (Clenching, Oral Mucositis, closed Eyes, DYspagia). This study aims to identify the prevalence of the COMEDY pattern among chemotherapy-induced OM.

Subjects and methods: Forty-two medical records of children undergoing chemotherapy for haemato-oncologic diseases and presenting OM were reviewed. The following data were collected: age, type of haemato-oncologic disease, presence of dysphagia, type of oral mucosal lesions (i.e. traditional oral mucositis or COMEDY pattern), site of oral lesions, ear-nose-throat (ENT) assessment for the indirect signs of NERD and paediatric neuro-psychiatric (PNP) assessment.

Results: Among 42 children with chemotherapy-related OM, 6 patients (14.2%) showed the COMEDY pattern. Besides the characteristic clinical aspect of the oral mucosa, initially classified as grade II OM, these children suffered from NERD-related dysphagia and PNP issues.

Conclusion: A COMEDY pattern can occur in a number of cases of chemotherapy-induced OM; recognizing this pattern may improve the effectiveness of treatment.

KEY WORDS

chemotherapy, children, dysphagia, mucositis

1 | INTRODUCTION

Oral mucositis (OM) is one of the most common debilitating complications in children receiving cancer therapy, occurring in 40%–80% of paediatric patients undergoing chemotherapy and/or radiotherapy. OM may manifest as erythema, oedema or painful ulceration associated with significant pain, dysgeusia and malnutrition, all of which worsen the patient's quality of life. In addition, oral mucositis represents a significant risk factor for systemic infections, particularly in neutropenic patients (Bardellini et al., 2013; Bardellini et al., 2016; Chen et al., 2004; Cheng et al., 2001; Scully et al., 2003). Several factors such as therapeutic regimen, duration of treatment, dose intensity, number of chemotherapeutic cycles and previous

episodes of mucositis influence the individual's risk of OM (Bardellini & Majorana, 2019; Clarkson et al., 2010; Lalla et al., 2008; Lalla et al., 2014; Majorana et al., 2015).

Recently, we reported a particular type of OM, associated with non-erosive reflux disease (NERD), whose features have been shortened in the acronym 'COMEDY' (Clenching, Oral Mucositis, closed Eyes, and DYspagia) (Bardellini & Majorana, 2019).

Children undergoing chemotherapy can experience NERD. Non-erosive reflux disease may manifest with laryngeal symptoms such as coughing, sore throat, hoarseness, dysphonia, dysphagia and globus (sensation of 'lump in throat'), as well as signs of laryngeal irritation during laryngoscopy (Baudoin et al., 2014; Farré, 2013; Richter, 2000; Vaezi et al., 2003). According to various studies, most patients with

NERD suffer from anxiety, depression or other emotional disorders (Faruqui, 2017; Javadi & Shafikhani, 2017; Li et al., 2018; Shaw et al., 2001). Dysphagia may induce teeth-clenching in response to pharyngeal pain, resulting in the formation of a traumatic oedema and a widespread milky appearance of the oral mucosa, with indentation marks on the cheeks (Bardellini & Majorana, 2019). Children show limited mouth opening and complain of pain, associated with a peculiar posture characterized by raised and hunched shoulders and closed eyes. This attitude could be linked to a defensive reaction due to pharyngeal pain, emotional distress and anxiety.

This study aimed to evaluate the prevalence of the COMEDY pattern among chemotherapy-induced OM in paediatric age.

2 | MATERIALS AND METHODS

This retrospective study was carried out through the revision of 70 medical records of children undergoing chemotherapy for haemato-oncological diseases at the Department of Paediatric Hematology/Oncology of Brescia from 2018 to 2020. The records of patients showing signs of oral mucositis (OM) were selected.

2.1 | Data collection

The following data were collected: age, type of haemato-oncologic disease, presence of dysphagia, type of oral mucosa lesions (i.e. oral mucositis or COMEDY pattern), site of oral lesions (buccal mucosa, tongue, gingiva, hard palate, soft palate or tonsil pillars), ear-nose-throat (ENT) assessment for the indirect signs of NERD and paediatric neuro-psychiatric (PNP) assessment.

2.1.1 | Oral mucositis scoring

Oral mucositis grade was scored according to the World Health Organization (WHO) grading system (WHO, 1976).

2.1.2 | Clenching, Oral Mucositis, closed Eyes, DYspatia pattern

A widespread opalescent milky appearance of the oral mucosa, with indentation marks on the cheek and/or on the tongue, associated to pain and dysphagia, was evaluated as a possible COMEDY pattern, to be confirmed after ENT and PNP assessments.

2.1.3 | Ear-nose-throat (ENT) assessment

Ear-nose-throat assessment was provided only when patients complained of laryngeal symptoms (chronic cough, chronic throat pain, dysphagia, dysphonia, change in voice, odynophagia, the sensation

of a lump in the throat). Typical NERD-related laryngoscopic findings were recorded, in particular (1) posterior laryngeal inflammation, oedema and erythema and (2) laryngo-tracheal stenosis, developed at the posterior commissure and the sub-glottic area and causing typical relapsing paroxysmal laryngospasm.

2.1.4 | Paediatric neuro-psychiatric (PNP) assessment

Paediatric neuro-psychiatric assessments were performed by a child neuropsychiatrist who routinely treats children.

Anxiety disorders were defined according to the International Classification of Diseases (ICD, currently version 10, World Health Organization) (WHO, 1993). Patients were diagnosed to suffer from PNP issues if they met the criteria of CDC-10, version 2019, F 32.0.

2.2 | Compliance with ethical standards

The study was planned and carried out in compliance with the Declaration of Helsinki and Good Clinical Practice, and it was approved by the Local Ethics Committee (NP4245).

3 | RESULTS

A total of 42 children (23 males, 19 females) aged 8.5 years old (range 1.1–17.1) showed chemotherapy-related OM (Table 1). Out of them, 6 patients (14.2%) presented a clinical aspect of the oral mucosa attributable to the COMEDY pattern (Figure 1–3). Overall, dysphagia was reported in 16 (38.1%) children. Of these children suffering from dysphagia, 6 were those with a COMEDY pattern (6/16); the remaining 10 patients presented oral mucosal lesions on the soft palate or on the tonsil pillars, classified as grade III (7/10) or IV (3/10) OM, which were most likely the cause of their dysphagia. NERD-related laryngoscopic findings were reported overall in 9 (21.4%) patients. All children with a COMEDY pattern (6/9) showed NERD-related laryngoscopic findings; out of the remaining 3 children, 2 had grade III OM without dysphagia and one complained of dysphagia and grade IV OM. Overall, PNP issues were reported in 7 (16.6%) children. All children with a COMEDY pattern showed PNP issues (6/7); the last remaining child had grade I OM, without any dysphagia or NERD. Finally, all children with a COMEDY pattern were affected by acute lymphoblastic leukaemia.

4 | DISCUSSION

This study describes a particular dysphagia-related OM in cancer children. Dysphagia is a debilitating, depressing and potentially life-threatening complication in cancer patients, that is likely underreported. It is related to a number of factors such as the direct impact

TABLE 1 Main findings of the study population ($n = 42$ children with OM)

Males: females	23:19	
Mean age	8.5 years (range 1.1–17.1)	
		Number of cases (n)/total cases (n) (%)
Disease		
	Acute lymphoblastic leukaemia	23/42 (54.8)
	Lymphoma	7/42 (16.7)
	Sarcoma	5/42 (11.9)
	Other	3/42 (7.1)
	Solid tumours	1/42 (2.4)
	Langerhans cell histiocytosis	1/42 (2.4)
	Acute myeloblastic leukaemia	2/42 (4.7)
Grading OM	I	3/42 (7.1)
	II	15/42 (35.7)
	III	21/42 (50)
	IV	3/42 (7.1)
Dysphagia		16/42 (38.1)
NERD		9/42 (21.4)
PNP issues		7/42 (16.7)
Dysphagia & NERD		7/42 (16.7)
Dysphagia & PNP issues		6/42 (14.2)
COMEDY pattern		6/42 (14.2)
COMEDY & Dysphagia		6/42 (14.2)
COMEDY & NERD		6/42 (14.2)
COMEDY & PNP issues		6/42 (14.2)

of the tumour, surgical resection, chemotherapy, radiotherapy and other therapies such as epidermal growth factor receptor inhibitors (Ribeiro et al., 2019). Most literature focuses on radiotherapy-related dysphagia, in which the direct damage of the exposed tissues is due to a cascade of inflammatory cytokines triggered by oxidative stress. The severity of radiation-induced dysphagia is dependent on total radiation dose, fraction size and schedule, target volumes, treatment delivery techniques, concurrent chemotherapy, genetic and psychological factors (Dysphagia Section, Oral Care Study Group, MASCC/ISOO, 2012).

Very few studies focus on chemotherapy-induced dysphagia. In a recent review, Ribeiro et al. (2019) concluded that the alterations in the swallowing function were more present in patients with hematologic tumours than with solid ones; however, the mechanism by which dysphagia occurs is not yet clear. Dysphagia could be caused by the presence of erosive lesions on the soft palate and/or tonsil pillars, or, in the absence of erosive lesions, by NERD-related pharyngo-laryngitis (Ribeiro et al., 2019).

Children undergoing chemotherapy can experience NERD, both for the therapeutic regimens and emotional distress. In some paediatric patients, NERD induces a defensive teeth-clenching reaction to the pharyngeal pain (Baudoin et al., 2014). Clenching causes a traumatic oedema of the oral mucosa, which becomes whitish with visible indentation marks (Bardellini & Majorana, 2019). Children complain of pain, present limited mouth opening and poor posture

with contraction of the neck muscles, lifting of the shoulders and forward bending of the head. Closed eyes and refusal to interact with others fall under the anxiety psychological status. All these elements configure a specific pattern, which includes Clenching, Oral Mucositis, closed Eyes and DYspagia, shortened in the acronym 'COMEDY'.

This retrospective study aimed to assess the prevalence of the COMEDY pattern, among chemotherapy-induced OM. Out of 70 screened records of children with haemato-oncological diseases, 42 (60%) patients suffered from chemotherapy-induced OM. Out of them, 6 patients (initially classified as grade II OM) had a COMEDY pattern (14.2%). All these cases presented widespread opalescent milky appearance of the oral mucosa (Figures 1–3), with indentation marks on the oral mucosa and/or on the tongue, associated to NERD-related dysphagia and PNP issues.

The COMEDY pattern can be considered a peculiar type of OM, which cannot be exclusively attributable to pharmacological toxicity but mostly to chronic traumatism induced by dysphagia and emotional distress (Bardellini & Majorana, 2019). Self-inflicted lesions are common in healthy adolescents (Amadori et al., 2017) and they are usually caused by emotional distress. In a recent study by (Amadori et al., 2017), they found 'morsication buccarum' (i.e. a chronic biting of the buccal mucosa which leads to wide desquamative areas on the mucosal surface) to be the most frequent self-inflicted traumatic lesion in adolescents. This lesion is common in patients with



FIGURE 1 Right oral mucosa: white lesions with indentation marks in a child with COMEDY pattern



FIGURE 2 Left oral mucosa: white lesions with indentation marks in a child with COMEDY pattern

anxiety, especially during periods of stress and intense studying. Nevertheless, clinically, it is different from the Comedy pattern, which is mainly caused by dysphagia and derives from a fixed and immobile clenching of the teeth, more similar to lesions found in adult bruxist patients.

All the COMEDY children were affected by acute lymphoblastic leukaemia; therefore, being they undergoing the same treatment plan, a pharmacological action inducing dysphagia could be considered. However, there were no visible posterior lesions in COMEDY



FIGURE 3 Tongue: white lesions with indentation marks in a child with COMEDY pattern

patients who complained of dysphagia, so the role of gastroesophageal reflux should be considered perhaps more significant than that of any specific drug.

Recognizing the COMEDY pattern in children undergoing chemotherapy could help to plan the correct treatment, taking into account the multifactorial etiopathogenesis of these mucosal lesions. As for treatment strategies, in addition to the use of oral mucosa coating agents, they should include the instruction on not biting one's mucosa and keeping teeth out of contact, conventional NERD therapy (i.e. proton-pump inhibitor) and psychotherapy to relieve depression and anxiety.

Mouthguards could be considered but their use would increase the risk of bacterial superinfection and therefore cause even more pain.

Further research is needed to establish the correct therapeutic protocol for children undergoing chemotherapy and presenting the COMEDY pattern.

AUTHOR CONTRIBUTIONS

Elena Bardellini: Writing – original draft. **Francesca Amadori:** Methodology; writing – original draft. **Federica Veneri:** Data curation; investigation. **Giorgia Albini:** Data curation; methodology. **Fulvio Porta:** Supervision. **Alessandra Majorana:** Supervision.

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CONFLICT OF INTEREST

None to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

- Amadori, F., Bardellini, E., Conti, G., & Majorana, A. (2017). Oral mucosal lesions in teenagers: A cross-sectional study. *Italian Journal of Pediatrics*, 43(1), 50. <https://doi.org/10.1186/s13052-017-0367-7>
- Bardellini, E., Amadori, F., & Majorana, A. (2016). Oral hygiene grade and quality of life in children with chemotherapy-related oral mucositis: A randomized study on the impact of a fluoride toothpaste with salivary enzymes, essential oils, proteins and colostrum extract versus a fluoride toothpaste without menthol. *International Journal of Dental Hygiene*, 14(4), 314–319. <https://doi.org/10.1111/idh.12226>
- Bardellini, E., & Majorana, A. (2019). Oral complications in children undergoing chemotherapy: The COMEDY (Clenching, Oral Mucositis, Eyes, DYspatia) pattern. *Journal of Pediatric Hematology Oncology*, 41(3), 249. <https://doi.org/10.1097/MPH.0000000000001347>
- Bardellini, E., Schumacher, F., Conti, G., Porta, F., Campus, G., & Majorana, A. (2013). Risk factors for oral mucositis in children receiving hematopoietic cell transplantation for primary immunodeficiencies: A retrospective study. *Pediatric Transplantation*, 17(5), 492–497. <https://doi.org/10.1111/petr.12094>
- Baudoin, T., Kosec, A., Cor, I. S., & Zaja, O. (2014). Clinical features and diagnostic reliability in paediatric laryngopharyngeal reflux. *International Journal of Pediatric Otorhinolaryngology*, 78(7), 1101–1106. <https://doi.org/10.1016/j.ijporl.2014.04.024>
- Chen, C. F., Wang, R. H., Cheng, S. N., & Chang, Y. C. (2004). Assessment of chemotherapy-induced oral complications in children with cancer. *Journal of Pediatric Oncology Nursing*, 21(1), 33–39. <https://doi.org/10.1177/1043454203259947>
- Cheng, K. K., Molassiotis, A., Chang, A. M., Wai, W. C., & Cheung, S. S. (2001). Evaluation of an oral care protocol intervention in the prevention of chemotherapy-induced oral mucositis in paediatric cancer patients. *European Journal of Cancer*, 37, 2056–2063. [https://doi.org/10.1016/s0959-8049\(01\)00098-3](https://doi.org/10.1016/s0959-8049(01)00098-3)
- Clarkson, J. E., Worthington, H. V., Furness, S., McCabe, M., Khalid, T., & Meyer, S. (2010). Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database Systematic Review*, 4(8), CD001973. <https://doi.org/10.1002/14651858.CD001973.pub4>
- Dysphagia Section, Oral Care Study Group, Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO), Raber-Durlacher, J. E., Brennan, M. T., Verdonck-de Leeuw, I. M., Gibson, R. J. H., Eilers, J. G., Waltimo, T., Bots, C. P., Michelet, M., Sollecito, T. P., Rouleau, T. S., Sewnaik, A., Bensadoun, R.-J., Fliedner, M. C., Silverman, S., Jr., & Spijkervet, F. K. (2012). Swallowing dysfunction in cancer patients. *Supportive Care in Cancer*, 20, 433–443. <https://doi.org/10.1007/s00520-011-1342-2>
- Farré, R. (2013). Pathophysiology of gastro-esophageal reflux disease: A role for mucosa integrity? *Neurogastroenterology & Motility*, 25(10), 783–799. <https://doi.org/10.1111/nmo.12201>
- Faruqui, A. A. (2017). Gastroesophageal reflux disease associated with anxiety: Efficacy and safety of fixed dose combination of amitriptyline and pantoprazole. *Gastroenterology Research*, 10(5), 301–304. <https://doi.org/10.14740/gr898e>
- Javadi, S. H. A. S., & Shafikhani, A. A. (2017). Anxiety and depression in patients with gastroesophageal reflux disorder. *Electronic Physician*, 9(8), 5107–5112. <https://doi.org/10.19082/5107>
- Lalla, R. V., Bowen, J., Barasch, A., Elting, L., Epstein, J., Keefe, D. M., McGuire, D. B., Migliorati, C., Nicolatou-Galitis, O., Peterson, D. E., Raber-Durlacher, J. E., Elad, S., & Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). (2014). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*, 120(10), 1453–1456. <https://doi.org/10.1002/cncr.28592>
- Lalla, R. V., Sonis, S. T., & Peterson, D. E. (2008). Management of oral mucositis in patients who have cancer. *Dental Clinics of North America*, 52(1), 61–77. <https://doi.org/10.1016/j.cden.2007.10.002>
- Li, X., Ding, F., Luo, P., Yang, J., Liu, Z., Liu, J., Zhang, Y., Leng, A., & Wu, K. (2018). Study on the therapeutic effects of drug and cognitive-behavioral therapy on non-erosive reflux disease patients with emotional disorders. *Frontiers in Psychiatry*, 9(9), 115. <https://doi.org/10.3389/fpsyg.2018.00115>
- Majorana, A., Amadori, F., Bardellini, E., Campus, G., Conti, G., Strohmenger, L., Schumacher, R. F., & Polimeni, A. (2015). Taste dysfunction in patients undergoing hematopoietic stem cell transplantation: Clinical evaluation in children. *Pediatric Transplantation*, 19(5), 571–575. <https://doi.org/10.1111/petr.12535>
- Ribeiro, I. L. A., Silva, S. M., Limeira, R. R. T., Bonan, P. F. R., Valença, A. M. G., Lima Neto, E. A., & Castro, R. D. (2019). Differences between the oral changes presented by patients with solid and hematologic tumors during the chemotherapeutic treatment. *Journal of Applied Oral Science*, 25(28), e20190020. <https://doi.org/10.1590/1678-7757-2019-0020>
- Richter, J. (2000). Extraesophageal presentations of gastroesophageal reflux disease: An overview. *American Journal of Gastroenterology*, 95(8 Suppl), S1–S3. [https://doi.org/10.1016/s0002-9270\(00\)01071-6](https://doi.org/10.1016/s0002-9270(00)01071-6)
- Scully, C., Epstein, J., & Sonis, S. (2003). Oral mucositis: A challenging complication of radiotherapy, chemotherapy, and radiochemotherapy: Part 1, pathogenesis and prophylaxis of mucositis. *Head & Neck*, 25(12), 1057–1070. <https://doi.org/10.1002/hed.10326>
- Shaw, M. J., Talley, N. J., Beebe, T. J., Rockwood, T., Carlsson, R., Adlis, S., Fendrick, A. M., Jones, R., Dent, J., & Bytzer, P. (2001). Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. *American Journal of Gastroenterology*, 96(1), 52–57. <https://doi.org/10.1111/j.1572-0241.2001.03451.x>
- Vaezi, M., Hicks, D., Abelson, T., & Richter, J. (2003). Laryngeal signs and symptoms and gastroesophageal reflux disease (GERD): A critical assessment of cause and effect association. *Clinical Gastroenterology and Hepatology*, 1, 333–344. [https://doi.org/10.1053/s1542-3565\(03\)00177-0](https://doi.org/10.1053/s1542-3565(03)00177-0)
- WHO. (1976). *Common toxicity criteria*. World Health Organization.
- WHO. (1993). *The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research*. World Health Organization.

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