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Literature Review

Dental Manifestations of Antitumor Therapy: Literature Review

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Abstract

Anticancer therapy is associated with a wide range of systemic symptoms, including oral pathologies, such as dry mouth, mucositis, masticatory spasm, osteoradionecrosis, dental caries, opportunistic infections, dysphagia, hypogeusia, dysgeusia, and hyposalivation. Dental professionals are the most qualified experts in the diagnosis and treatment of oral pathologies, as well as their prevention and control in cancer patients receiving radiation therapy or chemotherapy. The aim of the review was to assess domestic and international literature on primary oral complications associated with anticancer therapy. The review also aimed to highlight the importance of dental care in improving the quality of life of these patients, as well as to provide practical guidelines for managing these complications. The search was performed using electronic databases PubMed, eLIBRARY.RU, and Google Scholar. The search yielded 55 literature sources, which were included in the review.

Anticancer therapy may result in significant oral pathologies, including mucositis, infections, hyposalivation, changes in taste, and pain. These symptoms can affect various functions of the oral cavity and oropharynx, causing dry mouth and difficulties chewing and swallowing, which impairs nutrition. Moreover, they can affect speech, oral hygiene, denture treatment, and appearance, all of which can be detrimental to oral health, as well as social and emotional wellbeing. These side effects may also reduce compliance with anticancer therapy, affecting treatment outcomes, overall health, and therapy costs. When examining cancer patients, a dental professional must consider the prescribed therapy, as well as potential long-term complications similar to those in patients receiving bisphosphonates. As a result, a cancer patient will continue to receive the necessary treatment, and any new problems will be identified early.

Keywords: *Radiation Therapy; Chemotherapy; Complications; Oral Cavity; Dental Patients*

Introduction

In 2022, 624,835 new cases of malignant neoplasms (malignant neoplasms) were detected in Russia; of these, 283,179 in men and 341,656 in women), which is 7.6% higher than in 2021 (580,415 people) [1].

Cancer therapy is accompanied by a wide range of systemic manifestations, including dental manifestations, namely xerostomia, mucositis, muscular trismus, osteoradionecrosis, caries, opportunistic infections, dysphagia, hypogeusia, dysgeusia, and hyposalivation [2-4].

A dentist is the most qualified specialist in the field of diagnosis and treatment of oral cavity diseases, as well as preventive measures to control its condition in cancer patients undergoing radiation therapy or chemotherapy. That is why the integration of dentists into the process of providing care to cancer patients at all stages of the disease is extremely important [5].

Purpose of the Study

The purpose of the review is to analyze the domestic and foreign literature on the main dental consequences that may arise as a result of therapy prescribed for the treatment of oncological diseases. It is also necessary to emphasize the importance of dental care for improving the quality of life of such patients and, as a result, to provide practical recommendations for eliminating these consequences.

Materials and Methods

The search for primary sources was carried out in the electronic databases PubMed, eLIBRARY.RU and Google Scholar. Search queries included the following keywords and word-combinations in Russian and English: "radiation therapy", "chemotherapy", "oncology", "dentistry", "xerostomia", "mucositis", "muscular trismus", "osteoradionecrosis", "caries", "opportunistic infections", "dysphagia", "hypogeusia", "dysgeusia", "hyposalivation"; "radiation therapy", "chemotherapy", "oncology", "dentistry", "xerostomia", "mucositis", "muscle trism", "osteoradionecrosis", "caries", "opportunistic infections", "dysphagia", "hypogeusia", "dysgeusia", "hyposalivation". Search time interval: from the establishment of the relevant database to March 2024. After identification, before this screening, duplicates were excluded. At the screening stage, the authors analyzed the titles and abstracts of the identified articles for relevance to the topic of this review, as well as for the availability of a full-text version. At this stage, abstracts and letters to the editorial boards of scientific journals were excluded by the authors. 678 full-text articles were evaluated for admissibility. Inclusion criteria: publications in Russian or English; the study is published in a peer-reviewed scientific journal; The study describes dental complications of anticancer therapy and recommendations for their correction. All disagreements between the authors were resolved by consensus. In the end, 55 sources were included in this review (Figure 1).

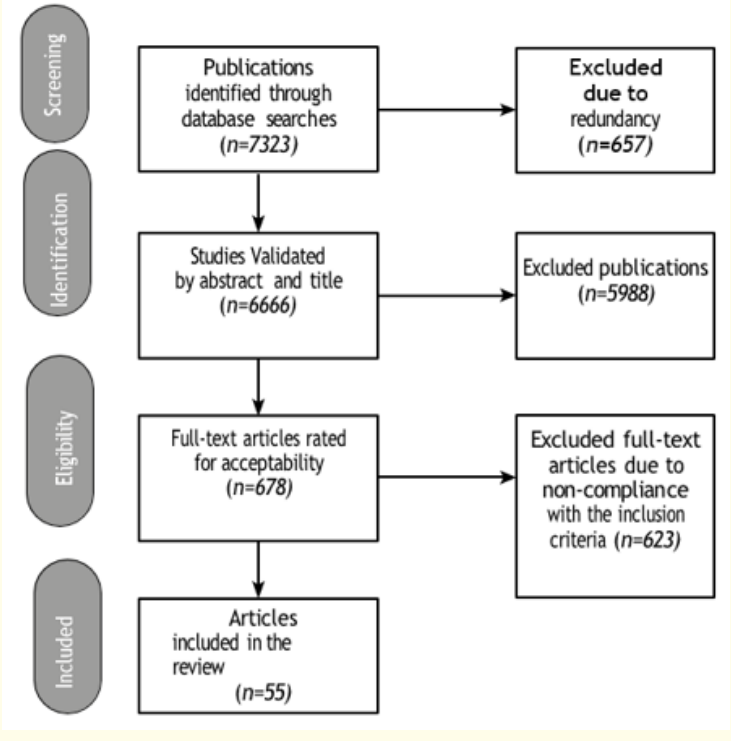

Figure 1: *The algorithm for selecting sources.*

Results and Discussion

Dental manifestations of tumor therapy

Radiation therapy (RT) is a method of basic or adjuvant therapy, widely used to treat malignant neoplasms in the head and neck area, improving the survival of patients [6]. It is important to take into account that radiotherapy can lead to damage to the oral mucosa, which is the result of the adverse effect of radiation not only directly on the mucous membrane, but also on the skin, salivary glands, bones, teeth and other components of the stomatognathic system [7,8].

Chemotherapy (CT), on the other hand, involves the use of chemotherapy drugs (CTPs) that prevent and/or control the growth of atypical cells by inhibiting their ability to divide. While the mucous membrane of healthy people is resistant to traumatization, chemotherapy predisposes to destructive changes in the mucosa, ulceration and the development of secondary infections [9]. Regardless of the purpose therapy, ionizing radiation and chemotherapy, alone or in combination, can significantly damage oral cavity structures and adjacent tissues [10].

Hyposalivation and xerostomia

A decrease in saliva secretion leads to hyposalivation, which leads to xerostomia, a subclinical condition characterized by complaints of dry mouth without a confirmed decrease in saliva production, which is one of the most common complications of head and neck radiotherapy [7].

Hypofunction of the salivary glands is directly related to the radiation dose and its volume. Therefore, the higher the radiation exposure, the worse the prognosis for xerostomia. Treatment of symptoms includes palliative measures [7,8].

Residual saliva becomes viscous, and due to a decrease in mucin content, its functions are impaired. A pronounced decrease in pH, due to changes in the concentration of calcium, sodium and bicarbonates, makes saliva more acidic. This change in salivation can contribute to an increased risk of infection of the oral cavity, the formation of bacterial plaque and the development of "ray caries", which disrupts the processes of chewing, swallowing, taste and speech [11].

Patients with xerostomia may experience a general burning sensation in the mouth, discomfort and redness in the area of the tip of the tongue. In order to prevent opportunistic infections, patients should be advised to use a 0.2 or 0.1% aqueous solution of chlorhexidine for rinsing the mouth. Fluoride should be used daily to combat radiation caries [12].

In the treatment of xerostomia caused by radiotherapy, patients are advised to avoid the use of substances that reducing salivation, especially tobacco and alcohol. It is recommended to rinse the mouth, drink water frequently, chew sugar-free gum and artificial saliva. Another solution may be to use salivary gland stimulants, such as 2% pilocarpine, which can provide greater comfort when chewing and swallowing [13]. In some patients with pilocarpine, pilocarpine hydrochloride is effective in stimulating saliva production, but it is only effective if the salivary glands are functionally intact [14]. glands, increasing saliva secretion. However, an acidic environment can lead to damage to oral tissues, exacerbation of mucositis, and also contribute to tooth demineralization [15].

Salivary gland function in patients undergoing radiotherapy is usually restored within 2-6 months or even a year after the completion of therapy. However, the deterioration can be irreversible, especially when the parotid glands are affected [16].

Fungal infections

Candida albicans is the most common microorganism that causes oral infections in patients undergoing anticancer therapy. Lesions of the oral mucosa caused by *C. albicans*, can manifest themselves in the form of white plaques, which, after removal, leave a reddish base.

Treatment of patients includes frequent mouthwash with chlorhexidine and topical antifungals such as ketoconazole and nystatin [17]. Chlorhexidine should be used at least 30 minutes before or after the use of any antifungal.

Viral infections

Viral infections with manifestations in the oral cavity or perioral area are a common complication of anticancer therapy. Immunosuppression observed in these patients makes them more susceptible to opportunistic infections [18]. Infection with herpes simplex virus (HSV) or its reactivation during myelosuppression in HSV-seropositive patients is one of the most common viral complications in cancer patients undergoing antitumor therapy [19]. The most common foci of HSV lesions are the red border of the lips and the skin of the perioral region. However, HSV can also manifest itself on the oral mucosa, usually limited to its keratinization.

The most common symptoms of HSV are pain, burning, itching, local temperature elevation, or redness of the affected epithelium. Lesions begin with the appearance of small erythematous papules that form vesicles that rupture lead to ulceration. Ulcers should be treated with topical preparations containing acyclovir, pressed tablets or lyophilized powder for infusion [19].

Bacterial infections

Hyposalivation disrupts homeostasis, contributing to a significant change in the microbial flora of the oral cavity, which leads to the occurrence of infections and increased reproduction of microorganisms. First of all, the transition from non-cariogenic microorganism to cariogenic ones is observed, with a predominant increase in the number of *Lactobacillus* and *Streptococcus mutans*. *Porphyromonas gingivalis*, associated with periodontal disease and root caries, also increase after radiotherapy [20,21]. Due to these factors, it is important to remove bacterial plaque while observing the rules of oral hygiene.

Radiation caries

Radiation caries (LA) is not a direct result of radiation exposure, but rather a consequence of hyposalivation and xerostomia. It can develop from 3 weeks to 1 year after radiotherapy. LA is characterized by rapid and early progression, usually in the cervical region of the tooth [22]. In addition to the direct effect of radiotherapy on the teeth, LC indirectly increases susceptibility to caries by reducing saliva secretion, changing its chemical composition and promoting the development of cariogenic microorganisms.

Hyposalivation is always accompanied by a change in eating habits and frequent consumption of soft, carbohydrate-rich foods, which further aggravates the course of caries [23]. If a lesion is found, its removal and restoration should be carried out immediately, given its rapid progression. If caries has reached the pulp, the root canal should be treated with its obliteration, leaving the root "buried" in the socket. Endodontic treatment eliminates pain and improves aesthetic and functional restoration of teeth, preventing osteoradionecrosis, as well as avoiding tooth extraction [24].

Oral hygiene should include home care and regular preventive visits to the dental office. Daily topical use of fluoride in the form of both mouthwash and neutral gel (1% sodium fluoride) is effective in the fight against caries [22].

Periodontal diseases

The periodontal ligament is also sensitive to the effects of radiation. X-ray can these changes increase the risk of periodontal disease, as they reduce the ability to repair and remodel. Therefore, recommendations for oral hygiene and procedures such as tartar removal and root planing are necessary and preferably should be followed before starting radiotherapy [25].

Anomalies of the dentofacial system

The use of chemotherapy in the phase of odontogenesis can alter the formation and development of dental rudiments by contributing to the shortening of premolar roots, the formation of conical roots of molars, premolars and canines, agenesis, microdontia, changes in root

formation, enamel hypoplasia and hypocalcification. given to children from birth to puberty can cause changes in bone growth, leading to skeletal-craniofacial anomalies (underdevelopment of the upper or mandibular region), as well as anomalies in the development of teeth [26].

Oral mucositis

Oral mucositis is one of the most frequent and early side effects resulting from antitumor therapy. Mucositis caused by chemotherapy is characterized by inflammation of the oral mucosa, with predominant damage to the non-keratinized epithelium [27]. At the same time, radiation-induced mucositis affects the surface of the mucous membrane directly facing the focus of radiation manifestations are similar and do not have significant differences in the clinical picture [9].

The first clinical manifestations of oral mucositis are redness and swelling of the mucous membrane. With the progression of the disease, tissue atrophy, wet desquamation, erythema formation, hyperkeratinization, ulceration and necrosis of the mucous membrane may occur lasting consequences. The period of manifestation of the erythema phase is very diverse. In chemotherapy, it usually manifests itself 4 - 5 days after drug administration. Meanwhile, in head and neck radiotherapy, the first symptoms appear after the accumulation of a radiation dose of 10 Gy, as a rule, in the 2nd weeks of treatment [28].

Initially, a patient with mucositis complains of burning, swelling, and pain when eating. As the condition worsens, constant pain occurs, which persists throughout antitumor therapy and for several weeks after it, gradually stopping between 2 and 3 weeks after the end of treatment [7].

The severity of pain syndrome in mucositis depends on the degree of tissue damage, the sensitivity of nerve receptors, as well as the production of mediators of inflammation and pain. Some authors argue that mucositis is more severe in patients who do not observe the rules of oral hygiene. In such cases, the action of opportunistic microorganisms further aggravates the damage to the mucous membrane, increasing the risk of pain and necrosis [29]. Other factors affecting the severity of mucositis include radiation dose, dosage and type of CTP, the patient's general health, and the use of local irritants such as alcohol, tobacco, and spicy foods [9].

Many substances, such as steroids, vitamin E, oral glutamine supplements, and cryotherapy, have been studied as methods of prevention and treatment of oral mucositis [30,31]. Palliative treatment includes topical/systemic analgesics, flaps of the mouth with solutions containing chlorhexidine to reduce the risk of infection, as well as benzydamine hydrochloride solution to relieve pain [17].

Photobiomodulation is an effective method of controlling the symptoms of oral mucositis. It promotes the release of prostaglandins, which has an anti-inflammatory effect. It also stimulates the release of endorphins, helping to control pain [32]. Laser therapy targets many markers of inflammation and reduces oxidative stress locally. growth factors that play an important role in the development of mucositis [32].

Most studies have demonstrated that laser therapy is effective in the treatment of oral mucositis. However, the parameters reported in the literature vary greatly [33,34]. Severe mucositis can limit the opening of the mouth, which makes it difficult to use the laser and extraoral effects are effective in the treatment of mucositis. Nevertheless, extraoral exposure can reduce the duration of laser therapy sessions by an average of 4 minutes [35].

All patients who develop oral mucositis from World Health Organization Grade I to IV should be treated with weekly laser therapy until the lesions heal completely. Prophylactic photobiomodulation is fundamental for all cancer patients. If possible, prophylactic therapy should be started 2 or even 3 weeks before the use of radiotherapy or chemotherapy It is important to follow the recommendations for oral hygiene, diet, quit smoking and alcohol. The sooner they are photobiomodulation and patient care are initiated, the better prepared he will be to confront aggressive antitumor therapy.

Hypogeusia and dysgeusia

Hypogeusia is a decrease or loss of the four main taste sensations. This condition can be observed after 2 weeks of radiotherapy. It is associated with increased sensitivity of the taste buds, especially the groove and mushroom papillae, which leads to partial or complete loss of taste during treatment. Lack of taste combined with pain, dysphagia, hyposalivation, and depression can lead to loss of appetite and malnutrition [22]. Hypogeusia can be constant, and in some cases dysgeusia may occur. As a preventive and therapeutic measure, patients with such complaints are recommended to be additionally prescribed zinc and copper preparations to reduce the severity of symptoms [36].

Trismus

Trismus of the masticatory muscles leads to difficulty opening the mouth, which prevents proper oral hygiene. Trismus is a relatively common complication after radiotherapy of the head and neck that occurs as a result of hypovascularization, edema, cell destruction, atrophy, and fibrosis of the irradiated muscle tissue [37]. Prevention and treatment of trismus include physiotherapy sessions, which should vary depending on the severity of the patient's condition [37,38]. A study by K.C. Bragante., *et al*. shows that in patients with head and neck tumors without physiotherapeutic intervention during RT, mandibular movements are limited. This indicates that the presence and severity of trismus should be assessed during RT, especially if the patient has reduced performance, irradiation of the oral cavity and oropharynx, and a nasoenteral probe is used [38].

Clinical studies of low-intensity laser therapy for trismus have shown a significant reduction in spasm of the masticatory muscles in patients immediately after its use [39]. However, low-intensity laser therapy does not replace traditional methods of treatment and can be used in combination with them, contributing to better clinical resolution [40].

Osteonecrosis

Osteoradionecrosis is one of the most serious and undesirable complications resulting from head and neck radiotherapy [23,37]. Its pathogenesis is associated with the formation of hypocellular and hypovascular tissue as a result of irradiation, followed by spontaneous or traumatic destruction of the oral mucosa, which leads to a non-healing process, and, ultimately, to bone sequestration [41].

Bisphosphonates and other antiresorptive drugs, such as denosumab, inhibit osteoclast differentiation and function and enhance apoptosis, leading to reduced resorption and bone remodeling. Osteoclast differentiation and function are essential for bone healing and remodeling in all areas of the skeleton. However, osteonecrosis occurs mainly in the alveolar process of the upper and alveolar part of the lower jaw [42].

The most commonly affected anatomical area is the lower jaw, which has a denser and more compact bone structure and less blood supply than the upper jaw. Clinically, this is characterized by exposure of necrotic bone, which is accompanied by such manifestations as severe pain, perforation of the cortical layer, fistula formation, superficial ulcerations and pathological fractures, which are not always associated with the infection. Radiologically, this manifests itself as a poorly defined radiolucent formation without sclerotic borders. X-ray contrast images can be seen in the presence of bone sequestration [43].

Treatment should include surgical intervention, wound debridement, antibiotic therapy and hyperbaric oxygenation. To perform removal after radiotherapy, a number of conservative measures must be taken. To ensure healing by primary tension, it is necessary to avoid removing the surrounding bone, minimize mucoperiosteal displacement and alveoloplasty, and perform proper suturing [44]. Some authors successfully use extremely high-frequency therapy, ozone therapy, erbium laser, and yttrium solid aluminum-laser in the complex treatment of drug-associated osteonecrosis of the jaw [45].

Poor dental condition, bone trauma, periodontal disease, combined chemotherapy (systemic immunosuppression) and tooth extraction are risk factors for osteoradionecrosis [23].

Given that bacteria probably play a fundamental role in the pathophysiology of osteoradionecrosis, antimicrobial photodynamic therapy has been proposed, which is effective against many microorganisms. In addition, photobiodynamic therapy is well known for its anti-inflammatory, analgesic, and biomodulatory effects, resulting in pain relief and accelerated healing [46].

Many studies show that photobiomodulation and antimicrobial photodynamic therapies offer significant benefits in contributing to the effective treatment of the disease. This therapeutic approach reduces the severity of lesions by acting as an additional treatment within the complex of clinical strategies. The beneficial effect of disease control and improvement in the quality of life of patients justify the use of these methods of treatment [47,48].

Neurotoxicity

Neurotoxicity is characterized by non-specific, persistent and continuous pain that can be caused by certain CTPs that cause functional/structural changes in the central and peripheral nervous system depending on the dose and duration of use. Despite the This complication is of great importance for dentistry, since neurotoxic manifestations resemble the pain experienced with pulpitis. Symptoms appear and disappear spontaneously, making diagnosis difficult. Neurotoxicity does not manifest itself on the teeth or mucous membrane. However, X-ray genographic examination often reveals a thickening of the periodontal ligament [19]. Treatment of neurotoxicity includes the prescription of systemic analgesics, and discontinuation of CTP often leads to the disappearance of symptoms.

Discussion

Measures for the prevention and treatment of oral diseases should be based on a comprehensive study of the patient's medical history, including an assessment of the results of blood tests, physical condition and diet. In this case, it is necessary to conduct a detailed examination of the hard and soft tissues of the oral cavity. During oral examination, it is extremely important to inform patients about possible oral complications that may occur during and after chemotherapy and/or radiotherapy. It is worth emphasizing the importance of oral hygiene and the need for dental treatment [49].

Oral cavity lesions during antitumor therapy, which include conditions such as mucositis, infections, hyposalivation, taste changes, and various pains, can be significant. These manifestations can disrupt many aspects of the functioning of the oral cavity and oropharynx, affecting the sense of taste, causing dry mouth, difficulty chewing and swallowing, and, as a result, affect nutrition. Moreover, they can have a negative effect on speech function, the ability to maintain oral hygiene, dental prosthetics, and a person's appearance, which can affect social and emotional well-being. These side effects can also affect adherence to planned anticancer therapy, potentially affecting the outcome of treatment, overall health, and the cost of treatment [50].

Antitumor therapy in children can lead to numerous dental complications, children are particularly vulnerable to the long-term effects of cancer treatment, as it is usually carried out during their most active growth and development. dysfunctions [51,52]. J. Lanzetti., *et al*. came to the conclusion that dental hygienists are the main figures in the management of patients within the framework of oral care programs for cancer patients [53]. They help prevent and manage the negative effects of cancer therapy, achieving a significant improvement in quality of life.

All cancer patients should undergo a second examination by a dentist from the moment of diagnosis. Before, during and after treatment, the patient should be under the supervision of a dentist. Regular visits help to reduce the risk of late side effects associated with antitumor therapy, as well as reduce their severity during treatment [54].

Patients with head and neck malignant neoplasms often have clinically significant levels of psychological stress, characterized by a combination of symptoms, including anxiety, depression, cognitive impairment, and changes in behavior. The psychological disorder can persist over time, accompanied by transient feelings of vulnerability, sadness, and fear. Moreover, it can develop into more severe conditions, including depression and anxiety [55].

According to the results of a longitudinal study, after 18 months of radiotherapy, the incidence of depression in cancer patients increased, which is associated with the presence of a tumor and side effects of therapy. On the other hand, the level of anxiety was higher before the start of treatment, decreased immediately after the start of radiotherapy, but returned to the previous level within a year after its completion [56].

Oral health is an essential component of quality of life. Cancer patients experience a variety of symptoms that affect their oral health and therefore their quality of life. Treatment of cancer pain is a critical issue. All health care providers must ensure timely and appropriate patient education and care. Symptoms and strategies that allow patients to better control their disease and its treatment [57].

Conclusion

The consequences of anticancer therapy make dental care a constant problem even after cancer remission has been achieved. The role of dentistry in the treatment of cancer patients goes beyond.

It is important to establish that all cancer patients undergo a systematic dental examination before starting treatment in order to avoid treatment restrictions that affect their quality of life. Already during anticancer therapy, it is necessary to continue monitoring in order to monitor the possible side effects of therapy. It is desirable to carry out as much as possible fewer targeted interventions. Supportive programmes and regular professional oral care procedures are essential to maintain the patient's long-term health. Support programmes include motivational conversations and oral hygiene training for patients, oral mucosal monitoring and professional care every 3 months. When examining cancer patients, the dentist should take into account the therapy the patient is receiving, and it is also important to pay attention to possible long-term effects, such as those that may occur in patients treated with bisphosphonates. In this way, the cancer patient will not stop receiving proper medical care, and any new problem will be diagnosed at an early stage.

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Conflict of Interest

The authors declare the absence of obvious and potential conflicts of interest associated with the research and publication of this article.

Contribution of the Authors

R.K. Esiev - Development of the concept and design of the study, scientific editing of the manuscript; A.R. Shakhabova - Development of the concept and design of the study, scientific editing of the manuscript; L.V. Tsokova - Data analysis and retrieval, writing the manuscript; A.A. Tsakoyeva - Data analysis, writing the manuscript; A.V. Tolpinsky - Data analysis, editing the text of the manuscript; Y.S. Zakharova - Data analysis, verification and approval of the text of the manuscript; N.M. Movsisyan - Writing the manuscript, obtaining factual data; I.I. Nabiev - Editing the text of the article, data analysis; I.A. Bazhaeva - Obtaining data, writing the text of the article; R.Sh. Dimaeva - Approving the final version of the manuscript, editing the text of the article.

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Volume 25 Issue 5 May 2026