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MELANOMA: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS AND THERAPEUTIC ADVANCES

MELANOMA: EPIDEMIOLOGIA, FISIOPATOLOGIA, DIAGNÓSTICO E AVANÇOS TERAPÊUTICOS

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ABSTRACT

Melanoma is an aggressive form of skin cancer, the incidence of which has increased globally in recent decades, especially in fair-skinned populations. This malignant neoplasm originates from melanocytes, the cells responsible for producing melanin, and is strongly associated with sun exposure, use of tanning beds, family history and genetic predisposition. Early recognition of melanoma is essential, as patient survival is directly related to the stage of the disease at the time of diagnosis. The identification of suspicious lesions, complemented by imaging methods and biopsies, is essential for an accurate diagnosis, allowing appropriate therapeutic interventions. The pathophysiology involves a complex interaction between genetic and environmental factors. Mutations in critical genes, such as BRAF, NRAS and KIT, play a crucial role in the development of the disease. These damages promote alterations in the DNA of melanocytes, leading to uncontrolled cell proliferation and tumor formation. In addition, melanogenesis, or melanin production, is closely related to the body's response to solar damage, being an attempt to protect against harmful radiation. However, this protection may be ineffective in individuals with a genetic predisposition to developing melanoma. Advances in treatment have been significant, especially in the last two decades. Therapeutic options include surgery, immunotherapy, and targeted therapies that specifically target mutations present in tumor cells. Immunotherapies, such as PD-1 and CTLA-4 inhibitors, have shown remarkable efficacy in promoting an immune response against the tumor, while BRAF and MEK inhibitors offer new hope for patients with melanomas that harbor specific mutations. These advances reflect a paradigm shift in the management of melanoma, aiming not only at survival but also at improving the quality of life of patients, highlighting the importance of continued research and the development of new personalized therapies.

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Keywords: Melanoma. Diagnosis. Epidemiology. Etiology. Treatment.

RESUMO
O melanoma é uma forma agressiva de câncer de pele, cuja incidência tem aumentado globalmente nas últimas décadas, especialmente em populações de pele clara. Essa neoplasia maligna se origina dos melanócitos, células responsáveis pela produção de melanina, e está fortemente associada à exposição solar, uso de câmaras de bronzeamento, histórico familiar e predisposição genética. O reconhecimento precoce do melanoma é fundamental, pois a sobrevida dos pacientes está diretamente relacionada ao estágio da doença no momento do diagnóstico. A identificação de lesões suspeitas, complementada por métodos de imagem e biópsias, é essencial para um diagnóstico preciso, permitindo intervenções terapêuticas adequadas. A fisiopatologia envolve uma complexa interação entre fatores genéticos e ambientais. Mutações em genes críticos, como BRAF, NRAS e KIT, desempenham um papel crucial no desenvolvimento da doença. Esses danos promovem alterações no DNA dos melanócitos, levando à proliferação celular descontrolada e à formação de tumores. Além disso, a melanogênese, ou produção de melanina, está intimamente relacionada à resposta do organismo ao dano solar, sendo uma tentativa de proteção contra a radiação nociva. No entanto, essa proteção pode ser ineficaz em indivíduos com predisposição genética para o desenvolvimento de melanoma. Os avanços no tratamento têm sido significativos, especialmente nas últimas duas décadas. As opções terapêuticas incluem cirurgia, imunoterapia e terapias alvo, que visam especificamente as mutações presentes nas células tumorais. As imunoterapias, como os inibidores de PD-1 e CTLA-4, têm demonstrado eficácia notável na promoção da resposta imune contra o tumor, enquanto os inibidores de BRAF e MEK oferecem novas esperanças para pacientes com melanomas que apresentam mutações específicas. Esses progressos refletem uma mudança de paradigma no manejo do melanoma, visando não apenas a sobrevida, mas também a melhoria da qualidade de vida dos pacientes, evidenciando a importância da pesquisa contínua e do desenvolvimento de novas terapias personalizadas.

Palavras-chave: Melanoma. Diagnóstico. Epidemiologia. Etiologia. Tratamento.

RESUMEN
El melanoma es una forma agresiva de cáncer de piel, cuya incidencia ha aumentado a nivel mundial en las últimas décadas, especialmente en poblaciones de piel clara. Esta neoplasia maligna se origina a partir de los melanocitos, células responsables de la producción de melanina, y está fuertemente asociada con la exposición solar, el uso de camas solares, antecedentes familiares y predisposición genética. El reconocimiento temprano del melanoma es fundamental, ya que la supervivencia del paciente está directamente relacionada con el estadio de la enfermedad en el momento del diagnóstico. La identificación de lesiones sospechosas, complementada con métodos de imagen y biopsias, es fundamental para un diagnóstico certero, que permita intervenciones terapéuticas adecuadas. La fisiopatología implica una interacción compleja entre factores genéticos y ambientales. Las mutaciones en genes críticos como BRAF, NRAS y KIT desempeñan un papel crucial en el desarrollo de la enfermedad. Este daño promueve cambios en el ADN de los melanocitos, dando lugar a una proliferación celular descontrolada y a la formación de tumores. Además, la melanogénesis, o producción de melanina, está estrechamente relacionada con la respuesta del organismo al daño solar, siendo un intento de protegerse contra las radiaciones nocivas. Sin embargo, esta protección puede resultar ineficaz en personas con predisposición genética a desarrollar melanoma. Los avances en el tratamiento han sido significativos, especialmente en las últimas dos décadas. Las opciones terapéuticas incluyen cirugía, inmunoterapia y terapias dirigidas, que se dirigen específicamente a las mutaciones presentes en las células tumorales. Las inmunoterapias, como los inhibidores de PD-1 y CTLA-4, han demostrado una eficacia notable para promover

la respuesta inmune contra el tumor, mientras que los inhibidores de BRAF y MEK ofrecen nuevas esperanzas para los pacientes con melanomas que albergan mutaciones específicas. Estos avances reflejan un cambio de paradigma en el manejo del melanoma, apuntando no sólo a la supervivencia, sino también a mejorar la calidad de vida de los pacientes, destacando la importancia de la investigación continua y el desarrollo de nuevas terapias personalizadas.

Palabras clave: Melanoma. Diagnóstico. Epidemiología. Etiología. Tratamiento.

1 INTRODUCTION

Melanoma is one of the most aggressive types of skin cancer, originating in melanocytes, the cells responsible for producing melanin. Despite representing a lower proportion of all skin cancer cases compared to basal cell and squamous cell carcinomas, melanoma stands out for its high mortality rate due to its remarkable ability to rapidly metastasize to other organs (Kalyan Saginala et al., 2021). The incidence of melanoma has shown a worrying increase globally, especially in regions with high exposure to ultraviolet (UV) radiation, such as countries at latitudes closer to the equator. This increase reflects both behavioral changes, such as greater use of tanning beds, and advances in diagnostic methods that allow for early detection of the disease (Garbe et al., 2022).

The clinical relevance of melanoma is multifaceted, involving not only the high associated mortality rate, but also the neurological complications that can arise in advanced stages of the disease, significantly impacting the quality of life of patients (Cohen et al., 2019). In addition, melanoma imposes a considerable burden on the systems of health due to the need for complex and costly treatments, especially in cases of therapeutic resistance and immune evasion by tumor cells (Eddy; Chen, 2020). The diversity of clinical presentations and the molecular heterogeneity of melanoma make diagnosis and treatment even more challenging, requiring personalized and interdisciplinary approaches (Garbe et al., 2022).

Given this scenario, the importance of continuous advances in the diagnosis and treatment of melanoma becomes evident. Current research focuses on developing more accurate experimental models to test new therapies, as well as identifying molecular markers that can predict treatment response and patient prognosis (E. Elizabeth Patton et al., 2021; Teixido et al., 2021). In addition, the most recent European guidelines emphasize the need for an interdisciplinary approach to melanoma management, integrating advanced molecular diagnostic techniques and innovative targeted therapies (Garbe et al., 2022).

This article aims to provide a comprehensive overview of melanoma, addressing its epidemiology, etiology, diagnostic methods, therapeutic options, and prognosis. By integrating the latest scientific evidence and clinical guidelines, it is intended to offer an in-depth understanding of the complexities of this disease, contributing to the improvement of clinical practices and encouraging future research in the area. With the increasing prevalence of melanoma and ongoing challenges in its management, it is crucial that healthcare professionals and researchers are up-to-date on the latest advances to optimize clinical outcomes and reduce the global burden of this aggressive disease (Jenkins; Fisher, 2021; Villani et al., 2022).

2 GOAL

The objective of this article is to gather information, through the analysis of recent studies, about the aspects inherent to melanoma, especially epidemiology, pathophysiology, diagnosis and therapeutic advances.

3 METHODOLOGY

A search was carried out for scientific articles indexed in the Latindex and MEDLINE/PubMed databases between 2019 and 2024. The descriptors used, according to the "MeSH Terms", were: melanoma, etiology, diagnosis and management. 3275 articles were found, according to the inclusion criteria: articles published in the last 5 years, full texts, free of charge, and type of study. Paid papers with a publication date in a period greater than the last 5 years were excluded from the analysis, selecting 14 articles relevant to the discussion.

4 EPIDEMIOLOGY

Melanoma is one of the most lethal types of skin cancer, and its global incidence has increased significantly in recent decades. Recent estimates indicate that approximately 325,000 new cases of melanoma are diagnosed annually worldwide, with more than 57,000 deaths attributed to the disease each year (Kalyan Saginala et al., 2021; Villani et al., 2022). The prevalence of melanoma varies considerably between different regions, being higher in countries with predominantly Caucasian populations and high sun exposure, such as Australia, New Zealand, and the United States (Garbe et al., 2022). In Australia, for example, the annual incidence rate exceeds 33 cases per 100,000 population, while in countries with less sun exposure, such as Japan, this rate is drastically lower, with about 1 to 2 cases per 100,000 population (József Tímár; Ladányi, 2022).

Among the main risk factors associated with the development of melanoma, exposure to ultraviolet (UV) radiation plays a central role. Prolonged exposure to the sun, especially at peak times, and the use of tanning beds are strongly related to increased melanoma incidences (Garbe et al., 2022). Individuals with fair skin, blond or red hair, light eyes, and a tendency to develop sunburn are especially vulnerable (Li et al., 2022). In addition, a family history of melanoma and genetic mutations, such as those in the CDKN2A gene, substantially increase the risk of developing the disease (Cohen et al., 2019; Guo; Wang; Li, 2021). Research also suggests that melanoma can develop in areas of the body less exposed to the sun, reinforcing the importance of genetic and biological factors in the etiology of the disease (Strahil Strashilov; Yordanov, 2021).

Analysis of historical trends reveals a significant increase in melanoma rates over the past 50 years. In countries such as the United States, the age-adjusted incidence rate increased by more than 50% between 1982 and 2011, reflecting both changes in sun exposure habits and better diagnostic practices (Jenkins; Fisher, 2021). However, there is evidence that in some regions with effective prevention campaigns, such as Australia, the incidence rate has begun to stabilize or even increase in the number of people in the country. decline in younger populations, suggesting that preventive interventions and behavioral changes are beginning to show impact (Teixido et al., 2021). However, melanoma mortality remains a challenge, with particularly high rates in countries with limited access to early diagnosis and appropriate treatment (Kalyan Saginala et al., 2021).

Regional differences in melanoma incidence and mortality rates can also be attributed to sociocultural and economic factors, such as access to health care and the adoption of preventive measures, such as the use of sunscreen and regular skin self-exams. Given the complexity of melanoma epidemiology, a coordinated global approach that addresses both primary prevention and early diagnosis and treatment is essential to reduce the burden of this disease at the population level (Eddy; Chen, 2020; Villani et al., 2022).

5 ETIOLOGY AND PATHOPHYSIOLOGY

The etiology of melanoma is multifactorial, involving a complex interaction between genetic and environmental factors. Among the main genetic factors implicated in the development of melanoma, mutations in the BRAF, NRAS, and KIT genes stand out, which play crucial roles in cell signaling and cell cycle control (Cohen et al., 2019; Li et al., 2022). Approximately 50% of cutaneous melanomas have mutations in the BRAF gene, the most common being the V600E mutation, which promotes the constitutive activation of the MAPK/ERK pathway, favoring cell proliferation and tumor survival (Eddy; Chen, 2020). Mutations in the NRAS gene, observed in about 15% to 20% of cases, also activate the MAPK pathway, although by a different mechanism. Mutations in the KIT gene are more frequent in mucosal and acral melanomas, and are associated with resistance to some targeted therapies (József Tímár; Ladányi, 2022).

In addition to genetic factors, exposure to ultraviolet (UV) radiation is one of the main etiological factors in the development of melanoma. UV radiation, both from the sun and from indoor tanning beds, causes direct DNA damage, resulting in the formation of pyrimidine dimers and other mutations that compromise the integrity of the genetic material of skin cells (Teixido et al., 2021). This accumulated damage leads to mutations in oncogenes and tumor suppressor genes, such as TP53, which is essential for cell cycle control and apoptosis (Guo;

Wang; Li, 2021). In addition, chronic exposure to UV radiation also induces local immunosuppression, weakening the ability of the immune system to eliminate potentially malignant cells. This process is particularly relevant in the early stages of neoplastic transformation (Strahil Strashilov; Yordanov, 2021).

Melanogenesis, the process of melanin production by melanocytes, is also closely related to the pathophysiology of melanoma. Although melanin has the function of protecting the skin against the harmful effects of UV radiation, the excessive accumulation of sun exposure can lead to changes in the function of melanocytes, promoting their transformation into malignant cells (Rebecca; Somasundaram; Meenhard Herlyn, 2020). Hyperactivation of melanocytes and uncontrolled proliferation contribute to the formation of melanocytic tumors (Jenkins; Fisher, 2021). Recent studies suggest that, in addition to genetic mutation, dysfunction in melanin production can alter the tumor microenvironment, facilitating melanoma progression (Li et al., 2022).

Finally, the cell signaling pathways involved in melanoma are crucial for understanding tumor progression. The MAPK/ERK pathway, activated by mutations in BRAF and NRAS, is one of the main responsible for cell proliferation and resistance to apoptosis (E. Elizabeth Patton et al., 2021). Another important pathway is PI3K/AKT/mTOR, which is involved in the regulation of cellular metabolism and tumor cell survival (GUO; WANG; LI, 2021). The activation of these pathways not only facilitates the proliferation of melanoma, but also promotes angiogenesis and the ability to invade and metastasize (Eddy; Chen, 2020). Thus, the detailed study of these pathways has been fundamental for the development of targeted therapies, which aim to block these signaling and contain the progression of melanoma (Villani et al., 2022).

6 DIAGNOSIS AND MOLECULAR MARKERS

Early diagnosis of melanoma is essential to improve prognosis and reduce mortality, and a combination of clinical and laboratory methods has been employed for this purpose. Dermoscopy is an essential tool in the clinical diagnosis of melanoma, allowing the visualization of specific patterns that differentiate benign from malignant melanocytic lesions. Studies indicate that dermoscopy increases diagnostic accuracy by up to 30% when compared to simple clinical examination (Garbe et al., 2022). However, diagnostic confirmation still depends on an excisional biopsy, in which the entire suspicious lesion is removed and histologically examined. Histopathological analysis is crucial to determine characteristics such as depth of invasion, which directly correlates with the risk of metastasis and tumor stage classification (Teixido et al., 2021).

In recent years, molecular tests have gained importance as complementary tools in the diagnosis of melanoma, especially in cases of atypical or recurrent lesions. Molecular markers, such as BRAF, NRAS, and KIT, are frequently used for differential diagnosis and risk stratification in patients with melanoma (József Tímár; Ladányi, 2022). The mutation in the BRAF gene, present in about 50% of cutaneous melanomas, is particularly useful to guide therapeutic decisions, since the presence of this mutation may indicate the use of specific inhibitors such as vemurafenib or dabrafenib. Similarly, mutations in NRAS and KIT not only aid in diagnosis but also provide valuable information about tumor behavior and expected response to targeted therapies (Garbe et al., 2022).

The development of new molecular diagnostic techniques has revolutionized the detection and management of melanoma. Next-generation sequencing (NGS) is one such innovation, allowing detailed analysis of multiple genes involved in melanoma carcinogenesis in a single test (Teixido et al., 2021). This technique not only identifies mutations in key genes, such as BRAF and NRAS, but also makes it possible to detect rare variants that can influence prognosis and therapeutic response. In addition, the analysis of circulating biomarkers, such as circulating tumor DNA (ctDNA), has emerged as a promising tool to monitor disease progression and detect recurrences in a less invasive way (Garbe et al., 2022).

The most recent European guidelines emphasize the importance of integrating molecular markers and advanced genetic testing in the diagnosis and treatment of melanoma. These guidelines recommend molecular testing in all patients with metastatic melanoma to determine the presence of mutations in BRAF, NRAS, and KIT, allowing personalization of therapies and significantly improving clinical outcomes. In addition, molecular profile analysis has been shown to be useful in risk stratification, especially in cases of thin or indeterminate melanomas, where clinical behavior may be unpredictable (Teixido et al., 2021). Thus, the combination of traditional diagnostic methods with the latest molecular approaches offers a comprehensive and effective strategy for the management of melanoma (József Tímár; Ladányi, 2022).

7 TREATMENT AND TARGETED THERAPIES

The treatment of advanced melanoma has evolved significantly in recent decades, with a combination of surgical approaches, immunotherapies, and targeted therapies. Traditionally, surgery is the first line of treatment for localized melanomas, especially when detected early. Complete excision of the primary lesion and, when necessary, resection of regional lymph nodes, aims to prevent disease progression. However, in cases of metastatic melanoma or melanoma in advanced stages, surgery alone is rarely sufficient, requiring the

addition of systemic therapies to control the disease and improve patient survival (Villani et al., 2022).

In recent years, immunotherapy has stood out as one of the major advances in the treatment of metastatic melanoma, particularly with the use of immune checkpoint inhibitors. Drugs such as anti-PD-1 (pembrolizumab, nivolumab) and anti-CTLA-

4 (ipilimumab) have shown promising results, significantly increasing survival in patients with advanced melanoma. The activation of the immune system to fight tumor cells represents a paradigmatic shift in melanoma management. Recent studies have shown that the combination of anti-PD-1 with anti-CTLA-4 improves response rates and overall survival compared to the use of these drugs alone. However, the immune toxicity associated with these combinations is still a clinical challenge, requiring close monitoring (Eddy; Chen, 2020; Villani et al., 2022).

Targeted therapies, particularly BRAF and MEK inhibitors, have revolutionized the treatment of patients with specific mutations. About 50% of melanomas have the BRAF mutation, making the use of BRAF inhibitors (vemurafenib, dabrafenib) an effective strategy (E. Elizabeth Patton et al., 2021). These drugs directly inhibit the abnormal signaling pathway, resulting in reduced tumor cell proliferation. However, like monotherapy, these drugs tend to lose efficacy over time due to acquired resistance. To overcome this obstacle, the combination of BRAF inhibitors with MEK inhibitors (cobimetinib, trametinib) has shown to be a promising approach, prolonging the response to treatment and delaying the development of resistance (Eddie; Chen, 2020).

In addition to the therapies already established, new therapeutic strategies are under development. The combination of immunotherapies with targeted therapies and the use of novel molecules that modulate the tumor microenvironment have been explored in clinical studies. For example, chimeric antigen receptor (CAR-T)-based therapies and inhibitors of novel signaling pathways, such as the PI3K-AKT pathway, show potential in preclinical studies and early clinical trials (E. Elizabeth Patton et al., 2021). These advances, coupled with the growing understanding of melanoma immune evasion, indicate that the future of melanoma treatment may include even more personalized approaches, integrating multiple therapeutic modalities to improve patient outcomes (Villani et al., 2022).

8 PROGNOSIS AND FUTURE CHALLENGES

The prognosis for patients with melanoma is largely influenced by the stage of the disease at the time of diagnosis, as well as the response to treatment. Melanomas are classified into stages I to IV, with stage I being characterized by a high survival rate, which

can exceed 90% in five years when treated early. In contrast, melanomas in more advanced stages (III and IV), which have metastases, demonstrate a significant decrease in survival rates, with rates of less than 30% at five years (Cohen et al., 2019). In addition to the stage, factors such as the size of the tumor, the presence of ulcerations, and the location of the melanoma also play crucial roles in determining the prognosis. Studies indicate that melanomas located in the extremities tend to have a better prognosis than those located in areas such as the trunk or face (Rebecca; Somasundaram; Meenhard Herlyn, 2020).

Complications associated with advanced melanoma, especially when metastatic, also have a significant impact on patients' quality of life and overall prognosis. Among the most common complications are neurological manifestations, which occur when melanoma spreads to the central nervous system (CNS). This spread can result in severe symptoms such as pain, seizures, and neurological deficits, as well as increasing the complexity of treatment. The physical and emotional complications associated with the treatment and diagnosis of melanoma can impact treatment adherence and quality of life, making it essential to develop interventions that consider the integral well-being of patients (Cohen et al., 2019).

Another major challenge in the treatment of melanoma is resistance to currently available therapies. Although BRAF inhibitors and immunotherapies have provided significant improvements in clinical outcomes, many patients develop resistance after an initial period of response. Mechanisms of resistance include activation of compensatory signaling pathways, additional mutations in tumor cells, and changes in the microenvironment Tumor. Understanding these mechanisms of resistance is crucial for the development of new therapeutic strategies that can reverse or prevent resistance, such as combinations of different classes of drugs and the use of biomarkers that can predict response to treatment (Rebecca; Somasundaram; Meenhard Herlyn, 2020).

Finally, it is evident that future directions in melanoma research need to focus on personalized approaches that consider the individual characteristics of each patient and their tumors. Implementing personalized therapies, which target not only the known mutations but also the unique molecular characteristics of each tumor, can lead to better clinical outcomes. In addition, new research exploring the combination of therapies, the use of cancer vaccines, and the manipulation of the tumor microenvironment are essential to address the persistent challenges in the fight against melanoma. The future of melanoma research and treatment lies in the integration of these strategies, aiming not only to prolong patients' lives but also to improve their quality of life (Cohen et al., 2019).

9 CONCLUSION

The increasing incidence of melanoma, particularly in fair-skinned populations, emphasizes the need for awareness and prevention, especially in relation to sun exposure and the use of tanning beds. Epidemiological data show that melanoma is one of the fastest growing neoplasms in the world, with alarming incidence rates in regions with high sun exposure. Thus, public education campaigns on sun protection and the importance of skin self-examination are essential for early detection. Early detection remains a crucial factor for prognosis, as rapid identification of suspicious lesions can mean the difference between effective treatment and disease progression. The stage of melanoma at the time of diagnosis is determinant for the clinical outcome; Patients with early-stage injuries have significantly better survival rates. Therefore, the implementation of screening programs and the training of health professionals to recognize early signs are essential to improve survival rates. The pathophysiology of melanoma, marked by genetic mutations and damage caused by ultraviolet radiation, illustrates the complexity of the development of this neoplasm. The role of mutations in genes such as BRAF, NRAS, and KIT not only provides insights into tumor biology but also opens doors for targeted therapeutic approaches.

The interaction between genetic and environmental factors underlines the need for public health strategies aimed at sun protection education and regular skin monitoring. In addition, continued research into the molecular mechanisms of melanoma may facilitate the development of more effective interventions. With regard to diagnosis and treatment, recent advances are promising. New imaging technologies, combined with more accurate biopsy methods, have improved the ability to detect early. Dermoscopy, for example, is a valuable tool that allows for a more detailed evaluation of skin lesions. In addition, innovations in therapies, including immunotherapy and targeted therapies, have transformed the melanoma treatment landscape, offering hope to patients and healthcare providers. The use of immunotherapeutic agents, such as anti-PD-1 and anti-CTLA-4, has demonstrated remarkable efficacy in increasing survival in patients with metastatic disease. Despite the challenges that remain, such as resistance to therapies and the need for personalized treatments, continued progress in the research and development of new therapeutic strategies promises to improve outcomes and quality of life for melanoma patients. Resistance to treatments, whether by tumor adaptations or by evasion of the immune system, requires a multifaceted approach that includes a combination of therapies and the development of new drugs. Thus, the future of melanoma treatment is directed not only towards greater efficacy, but also towards the personalization of therapies, taking into account the individual characteristics of each patient and the biology of the tumor. Finally,

continued commitment to research and innovation is key in combating melanoma. The search for better diagnostic methods, in-depth understanding of pathophysiological mechanisms, and the development of more effective therapies represent essential steps to improve clinical outcomes and quality of life for patients affected by this devastating condition.

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