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Immunosenescence in Testicular Cancer Survivors: Potential Implications of Cancer Therapies and Psychological Distress

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Testicular cancer (TC) is the most frequent solid tumor diagnosed in young adult males. Although it is a curable tumor, it is frequently associated with considerable short-term and long-term morbidity. Both biological and psychological stress experienced during cancer therapy may be responsible for stimulating molecular processes that induce premature aging and deterioration of immune system (immunosenescence) in TC survivors, leading to an increased susceptibility to infections, cancer, and autoimmune diseases. Immunosenescence is a remodeling of immune cell populations with inversion of the CD4:CD8 ratio, accumulation of highly differentiated memory cells, shrinkage of telomeres, shift of T-cell response to Th2 type, and release of pro-inflammatory signals. TC survivors exposed to chemotherapy show features of immunological aging, including an increase in memory T-cells (CD4+ and CD8+) and high expression of the senescence biomarker p16INK4a in CD3+ lymphocytes. However, the plethora of factors involved in the premature aging of TC survivors make the situation more complex if we also take into account the psychological stress and hormonal changes experienced by patients, as well as the high-dose chemotherapy and hematopoietic stem cell transplantation that some individuals may be required to undergo. The relatively young age and the long life expectancy of TC patients bear witness to the importance of improving quality of life and of alleviating long-term side-effects of cancer treatments. Within this context, the present review takes an in-depth look at the molecular mechanisms of immunosenescence, describing experimental evidence of cancer survivor aging and highlighting the interconnected relationship between the many factors modulating the aging of the immune system of TC survivors.

Keywords: immunosenescence, cancer therapy, chemotherapy, psychological distress, testicular cancer survivors

INTRODUCTION

Testicular cancer (TC) is the most frequent solid tumors in males, accounting for 1–1.5% of all cancers in men. Its incidence is increasing worldwide. Although TC affects relatively young men (between the ages of 20 and 40), it is a curable tumor with a 5-year survival rate of 98% for localized disease (1, 2). Successful management of TC is based on both the correct use of diagnostic tools (including tumor markers) and the selection of the appropriate treatment. In patients with localized disease, surgical treatment may be curative, while in case of recurrent or metastatic disease, platinum-based chemotherapy regimen is the therapy of choice (3, 4). Moreover, patients with progressive disease could receive standard- or high-dose chemotherapy as second line (5–8). In case of high-dose chemotherapy, autologous hematopoietic stem cell transplantation (HSCT) is necessary to restore bone marrow function. The use of high-dose chemotherapy is associated with a high rate of long-term remissions (7–10), however, there are still no prospective studies that have demonstrated an advantage of one chemotherapy approach over another, and both standard-dose and high-dose treatment represent two valid options for patients with relapsed disease (11, 12).

Although the high response rate, TC survivors could develop short- and long-term morbidity. The early onset of age-related diseases and the expression of biological markers indicative of precocious aging of the immune system (known as immunosenescence) have been hypothesized as consequences of the stress caused by the many challenges faced by patients during the course of the disease (including aggressive therapeutic regimens and psychological distress) (13–17).

Given that TC survivors generally have a good life expectancy, their quality of life must be guaranteed. Addressing the long-term effects of TC treatments and the correlated molecular events is thus an important part of patient management. In this review, we focus on the phenomenon of immunosenescence and its mechanisms, contextualized to the types of cellular stress that may affect TC survivors.

HALLMARKS OF IMMUNOSENESCENCE

Immunosenescence or immune aging is the functional decline of the adaptive and innate immune systems generally associated with aging (18, 19). During youth, the immune system is quiescent in normal conditions but promptly responds to antigen stimulation. In contrast, the immune system of the elderly is in a state of mild activation and it is not able to adequately response to stimulation. This leads to a chronic pro-inflammatory state that reduces the immune competence of the individual and, from a clinical point of view, it is correlated with a higher rate of morbidity and mortality (19, 20).

Immunosenescence has been widely reported in aged individuals, as a result of the chronic antigen stimulation and cellular stress encountered throughout life (21–23). However, other factors are also associated with the acquisition of precocious senescent features in immune cells, including tissue damage, oxidative stress, cytotoxic therapies, DNA damage, chronic inflammation, and chronic psychological stress (13, 24, 25) (**Figure 1**).

The adaptive response is the immune compartment most widely affected by immunosenescence, with T cell functions undergoing profound and consistent changes during aging (21, 23). A progressive decline in T cell clone expansion in bone marrow and thymus induces a decrease in the number of

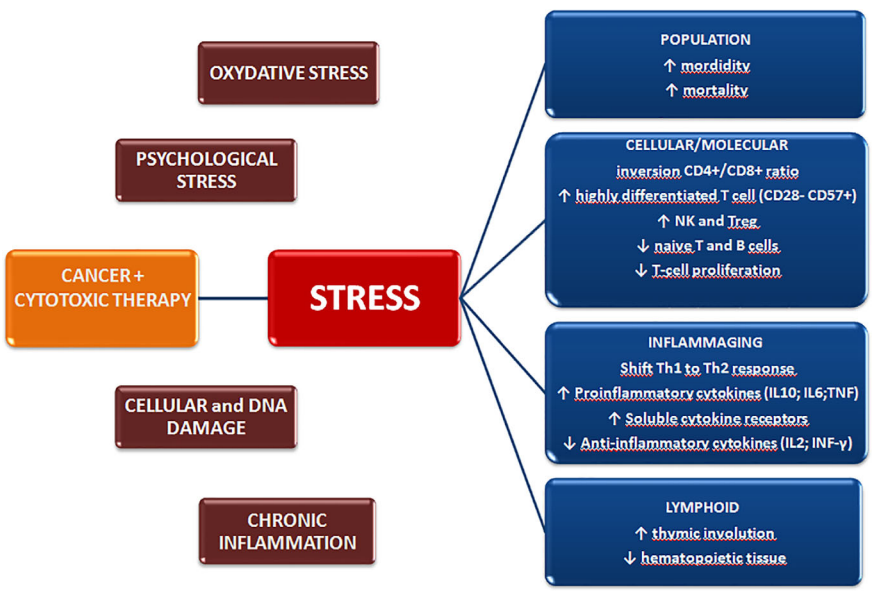

FIGURE 1 | Cancer diagnosis and treatment induce biological and psychological stressors that may promote premature aging of the immune system and exert long-term effects on the quality of life.

naïve T lymphocytes. Thymic involution occurs, leading to a progressive decrease in the naïve T-cells exiting the thymus (26, 27). Although the underlying mechanism of this regression is not fully understood, it is believed to be correlated with hormonal changes, oxidative stress, and infections (27, 28). Peripheral expansion is also reduced during aging, mainly due to repetitive stimulation by antigens, which induces a progressive differentiation of T cells. Highly differentiated T cells lose the costimulatory molecule CD28, necessary for TCR signaling, and accumulate features of senescence (*i.e* CD57 and KLRG1), with late-differentiated cells reaching the limit of replication (29) and acquiring markers of senescence (in particular, increase in p16INK4a in peripheral blood CD3+ cells and in SASP phenotype in both T and B cells) (30–33). This results in the filling of immunological space with T-cells with reduced proliferation ability, that secrete pro-inflammatory cytokines (*e.g.* IL10, IL6, and TNF) and that has a reduced T-cell receptor (TCR) repertoire (21, 23, 34). It has also been seen that T-cells may acquire new functions, such as suppressive activity and higher cytotoxic potential (29, 35–38).

Generally, aging brings about an increase in CD8+ T-cells, leading to a decrease in the CD4+/CD8+ ratio as CD4+ T-cells appear to be more resistant to age-related changes. However, an increase in late-memory CD28-negative cells has also been reported in the CD4+ compartment (35, 39, 40). It has been seen that alterations in T-cell functionality may influence polarization of T-helper cells, with a shift in the Th1/Th2-balance to a predominantly Th2 phenotype. In fact, lymphocytes from older individuals produce low levels of the Th1 cytokines IL-2, IFN-γ, and IL-12, while higher levels of the Th2 cytokines, IL-4, IL-5, IL-6, and IL-10 are secreted. This contributes to the altered immune response and to the higher susceptibility to infections seen in elderly people (41).

Several other alterations occurring during aging have also been reported in the B cell compartment, *e.g.* a decrease in naïve B cells and an accumulation of memory CD27 lymphocytes. Moreover, an increase in autoreactive antibody production and a decrease in the BCR repertoire are seen during aging, reflecting the greater susceptibility to autoimmune diseases and the lower responsiveness to infections and vaccinations of the elderly (42).

Immunosenescence is also known to affect innate immunity. Macrophage precursors decrease during aging and show telomere length reduction with decreased secretion of GS-CSF and other cytokines (*e.g.* TNF-alpha and IL-6) (43). Conversely, the number of neutrophils is preserved in the elderly despite the reduction in CD16 Fc expression, indicating an impairment of phagocytosis and of the generation of super-oxide mediated by CD16 Fc receptors (44). Moreover, the cytotoxic activity of natural killer (NK) cells decreases, marked by a reduced interferon secretion, which may affect their ability to eliminate tumors or viral-infected cells (45). Finally, expanded features of immunosuppression have recently been identified during the aging process. Increased numbers of circulating myeloid-derived suppressor cells (MDSCs) and regulatory T-cells (Tregs) have been reported in older mice and humans, further inhibiting the antigen-induced activation of helper and cytotoxic T cells (46, 47).

In brief, immunosenescence is caused by a complex remodeling of all the components of the immune system that may impair its ability to mount an effective defense. Whilst this process is unavoidable during physiological aging, several other pathological conditions may also be capable of impairing immune function.

EFFECT OF CANCER TREATMENT REGIMENS ON IMMUNOSENESCENCE

There is increasing evidence that some cancer treatments may induce cellular senescence and aging of the immune system, with implications for the development of secondary medical conditions later in life (13) (**Table 1**). Cytotoxic drugs (including cisplatin, alkylating agents, and anthracyclines) and radiotherapy have been shown to cause cellular senescence in both *in vitro* and *in vivo* models (59–61), with induction of DNA damage, epigenetic alterations and telomere attrition (13, 50, 62). A longitudinal study on breast cancer survivors treated with surgery, radiotherapy or chemotherapy showed that cytokine levels (TNF-alpha and IL-6) were significantly higher in patients than in untreated controls 6 and 18 months after the end of the primary cancer treatment (51). Moreover, expansion of memory T-cell CD28- CD57+ and increment of epigenetic aging were reported after radiotherapy alone or in combination with chemotherapy in breast cancer patients (15, 52), while accumulation of CD57+ T cell was observed in colorectal patients (49). More recently, a study conducted on 60 pediatric-adolescent cancer survivors revealed a higher expression of p16INK4 in CD3+ cells in patients than in the age-matched healthy population 5–6 years after the end of chemotherapy. The increased senescence was associated with the intensity of chemotherapy regimens and the severity of the frailty phenotype of the patient (60).

HSCT may also play a role in the induction of immunosenescence in that it induces replicative stress in transplanted stem cells whose job is to reconstitute the immune system (63), causing them to undergo accelerated aging. Consequently, the prevalence of myelodysplasia and secondary malignancies increases after HSCT (64). An increase in senescent features and a reduction in cytokine production have been reported in T-cells of pediatric patients undergoing HSCT (48). Moreover, some studies have analyzed the effect of HSCT combined with total body irradiation or high-dose chemotherapy on the immune system of cancer patients. High-dose chemotherapy combined with autologous stem cell transplantation has been associated with low number of naïve and accumulation of CD28- T-cells, and high expression of senescence markers was detected in CD3+ cells several years after the end of treatment (53, 55). Additionally, chemotherapy in combination with total body irradiation and HSCT has been associated with long-term epigenetic alterations of genes responsible for immune/inflammatory processes and oxidative stress (16). To date, only one paper has described the recovery of the immune system after chemotherapy and HSCT (57).

TABLE 1 | Reports of immunosenescence phenotype associated with cancer treatment.

Reference	No. cases	Cancer type	Time after treatment	Group comparison	Immunosenescence evidence
Daniel et al. (16)	44	Pediatric cancer	>10 years	ChT+RT+HSCT *vs* ChT	Accelerated epigenetic aging of T cells and increased production of Th1 cytokines in the irradiated cohort
Lee et al. (48)	21	Pediatric/young adult cancer and other non-malignant diseases	1–3 years	Donor *vs* recipient after allogeneic HSCT	Expansion of senescent T cells (CD28– or CD57+) in recipients, and decrease in ability of cytokines to produce CD4+ cells
Smitherman et al. (49)	69	Pediatric cancer	5–6years	ChT *vs* healthy controls	Increased p16INK4a expression in CD3+ cells of cancer survivors. Positive correlation between p16INK4a expression and patient frailty
Song et al. (50)	2,427	Pediatric cancer	>5 years	ChT, RT *vs* healthy controls	Telomere length was lower in cancer survivors and was associated with chronic health conditions
Alfano et al. (51)	315	Breast cancer	6–18months	ChT, RT *vs* healthy controls	Higher TNF-alpha and IL-6 in treated patients
Onyema et al. (15)	21	Breast cancer	6 months	ChT, RT *vs* healthy controls	Decrease in number of T cells and accumulation of CD28– CD57+ CD8+ T cells in treated patients
Sehl et al. (52)	72	Breast cancer	18 months	Pre- *vs* post-RT or ChT+RT	Increased senescent T cells and epigenetic aging after treatment
Fagnoni et al. (53)	120	Breast cancer	3–5 years	ChT + HSCT *vs* healthy controls	Decrease in number of naive T-cells and higher percentage of CD28– T cells in cancer survivors
Sanoff et al. (54)	33	Breast cancer	3-12 months	Post-ChT *vs* pre-ChT	Higher p16INK4a expression in CD3+ cells after ChT
Wood et al (55).	63	Hematologic malignancies	6 months	Pre- *vs* post-allogeneic or autologous HSCT	Higher p16INK4a expression in CD3+ cells after HSCT, higher p16INK4a expression in allogeneic *vs* autologous HSCT
Bruni et al. (56)	58	Colorectal cancer	ns	ChT-treated *vs* naive patients *vs* healthy controls	Increase in terminally differentiated TEMRA Vδ2pos T cells (CD27–, CD57+) in ChT-treated patients
Laznickova et al. (57)	36	Neuroblastoma	1–4years *vs* >5years	ChT, RT, HSCT *vs* healthy controls	Lower frequency of naıve CD8+ T and higher percentage of CD57+ memory T cells 1–4 years after treatment. At later time point (>5 years), T cell ratio was restored
Bourlon et al. (58)	16	Testicular cancer	3–192 months	ChT *vs* healthy controls	Lower percentage of T-cells, higher number of senescent (CD57+) T-cells and higher p16INK4a expression in CD3+ cells of cancer survivors

ChT, chemotherapy; RT, radiotherapy; HSCT, hematopoietic stem cell transplantation; ns, not specified.

Lázničková et al. reported that, although pediatric patients with neuroblastoma showed features of immunosenescence at early time-points (1–4 years) after treatment, they also began to show signs of immune reconstitution 5 or more years after diagnosis (57). However, the possibility of premature aging of the immune system at later time-points cannot be excluded and, as already stated, recovery has not been reported in survivors of other cancer types (16, 50, 49).

Only one study has been conducted to date on the long-term effects of chemotherapy on the immune system of TC survivors (58). Bourlon et al. compared TC patients undergoing chemotherapy (≥3 cycles of PEB) with a cohort of healthy age-matched men, reporting that cancer patients had significantly lower levels of T cells and CD4+ cells in total lymphocytes than the control group. Increase of memory cells number was detected in both CD4+ and CD8+ compartments, whereas memory B cells unexpectedly decreased. Moreover, CD3+ cells expressed higher levels of p16INK4a, suggesting the induction of a senescent phenotype (58). Even if few cases were analyzed, this is the first study to identify an aged immune system phenotype in TC survivors. Additionally, a correlation between a higher systemic inflammation index and poor prognosis was reported in TC patients, especially in relation to PDL1 expression (65). However, further studies are needed to address the role of other factors specific to a TC context (*e.g.* residual serum platinum levels, psychological stress, and different therapeutic schedules) in the aging phenotype.

PSYCHOLOGICAL STRESS AND INDUCTION OF IMMUNOSENESCENCE

The majority of TC survivors report good physical functioning and a relatively high health-related quality of life (66). However, as TC is acknowledged as both a highly distressing and potentially traumatic life event, it may override an individual's perceived ability to cope with the disease, eliciting emotional, behavioral, and physiological reactions that generate conditions of acute and chronic stress (67–69). The typically young age of patients at diagnosis and the existential challenge of a life-threatening disease and physical complications can interfere with psychological well-being both during and after treatment, inducing psychological distress and morbidity (65). The levels of psychological distress in TC survivors are higher than in noncancerous reference populations, with a more prevalent and severer anxiety (between 9 and 27%) and a greater fear of cancer (70–74). In most studies, depression in TC survivors appeared no more prevalent than in the general population although an Australian study did find higher rates of, and

more severe, depression in TC survivors than population norms (73). Cancer-related stress symptomatology such as post-traumatic stress disorder (PTSD) is among the long-term psychological effects of TC. This disorder includes intrusive ideation, hyper activation, re-experimentation, and avoidance. Dahl et al. observed PTSD in 10.9% of long-term TC survivors at an average of 11 years after diagnosis (75). Psychological stress is known to modulate the immune response and can partially suppress certain aspects of immune function (76, 77). Psychological distress and morbidity in both cancer survivors and the general population can lead to negative changes in bio-behavioral responses (78), inducing detrimental effects on immune health and function and immunological aging (79, 80). In particular, chronic stress, emotional distress, and social difficulties are associated with increased sympathetic nervous system signaling, hypothalamic pituitary adrenal axis dysregulation, inflammation, and decreased cellular immunity. These alterations in physiological adaptation systems are important risk factors for the development and progression of a wide range of physical and mental disorders (14, 79, 81–83).

In a meta-analysis, Segerstrom and Miller found that psychological strain or stress modifies the capacity and regulation of the immune response system and that the consequences of the stressful event vary on the basis of temporal parameters (acute *vs.* chronic) and the type of event (trauma *vs.* loss) (84). Stressful life events and associated negative emotions such as anxiety and depression affect the immune response by altering the sensitive interaction between the central nervous and hormonal systems and the immune system itself (85–88). Prolonged psychological stress appears to be correlated with cellular aging, inducing characteristic senescence features such as increased oxidative stress, reduced telomere length, chronic exposure to glucocorticoids, decreased thymus, changes in cell trafficking, decreased cell-mediated immune response, steroid resistance, and chronic low-grade inflammation (14, 89, 90).

Another important aspect of the relationship between cancer-derived psychological distress and immune system alterations is the fact that exposure to a traumatic event may increase the risk of psychiatric disorders and psychopathological suffering. It is believed that inflammation, one of the hallmarks of immunosenescence, contributes to this (91–93).

Recently, some studies have shown a clear association between PTSD and accelerated cellular senescence, as indicated by decreased telomere length, increased levels of inflammatory cytokines, enhanced T cell responses, a lower frequency of naïve CD8+ T-cells, and a rise in central memory and effector CD8+ T cells (94–96). In addition, symptoms of PTSD have been shown to more frequently associated with an aged immune phenotype characterized by a higher effector memory to naïve CD4+ and CD8+ T cell ratio (96–98).

The relationship between the psychological distress of TC survivors and changes in the immune system has not been widely investigated. However, given that cancer is undoubtedly one of the most stressful events in a person's life, placing demands on psychological adaptation during treatment and also throughout cancer survivorship (99), studies focusing on the correlation between psychological distress and immunosenescence in TC survivors are warranted.

STRESS-INDUCED IMMUNOSENESCENCE IN TESTICULAR CANCER SURVIVORS

TC survivors have an increased risk to suffer of late adverse events, including hypogonadism, infertility, metabolic syndromes, neurotoxicity, lower cognitive functions, reduced renal function, heart disease, and secondary cancers (100).

Although cisplatin-based chemotherapy is highly effective against TC, its long-term negative effects on healthy tissue have also been reported. In fact, whilst plasma platinum levels show a rapid decline from 1 to 3 years after chemotherapy, platinum has also been detected in the blood up to 20 years after treatment. In TC survivors, platinum concentrations correlated with the cisplatin dose used during therapy have been associated with neurotoxicity and other long-term adverse consequences (101–103). Within this context, it is important to underline the importance of the effects of treatment on a physical level (104), including erectile dysfunction (105), reduction in sexual activity (106), and loss of desire (107). In particular, a correlation between previous chemoradiotherapy and radiotherapy and the risk of erectile dysfunction was recently confirmed by a Danish study on a cohort of 2,260 TC survivors (108). As chemotherapy has a greater impact on Leydig cells than surgery or radiotherapy, TC survivors have a higher risk of hypogonadism (with increasing serum luteinizing hormone concentrations and decreasing serum testosterone levels) (109). A Norwegian study identified four risk factors for the development of hypogonadism, *i.e.* orchiectomy, testicular dysgenesis syndrome, treatment after orchiectomy, and aging (110). This risk was higher in the cohort undergoing chemotherapy than in other cohorts, with luteinizing hormone (LH) levels remaining very high in the former at 20 years. Moreover, the alteration in testosterone and LH levels accelerated over time, leading to the hypothesis of a reduced reserve capacity that worsens as time passes (110).

Hypogonadism also increases the risk of developing metabolic syndrome, including cardiovascular complications and diabetes, which appears to be greater after combination therapy (chemo-radiotherapy) (111, 112). Research is currently underway to evaluate the impact of testosterone administration in long-term TC survivors, but results are still somewhat discordant (113–116).

Moreover, studies focusing on the risk of developing diabetes have reported a potential correlation between low testosterone levels and changes in the immune system. In fact, lower testosterone levels are associated with central adiposity and insulin resistance (117), both of which are frequently involved in inflammatory and oxidative processes and endothelial dysfunction. Liao et al. demonstrated that testosterone levels

inhibit inflammation mechanisms (including the TNF-pathway), leading to a modulation of endothelial cell function and promoting wound-healing and angiogenesis. A fundamental role is played by the androgen receptor in this process (118). However, its relationship with metabolic syndrome is unclear (119, 120). Inflammatory states and stress may also be important conditions that lead to cytokine secretion (in particular, IL-6 and CRP), with a subsequent impact on aging. Maggio et al. hypothesized a correlation between low testosterone levels and increased secretion of pro-inflammatory cytokines in the genesis and maintenance of chronic diseases (121).

Several studies have been carried out to evaluate the correlation between treatment-related immunosenescence and the risk of a second cancer in TC survivors, some confirming a higher risk in patients undergoing chemotherapy and radiotherapy than in those treated with surgery alone. Second tumors have mainly been found in organs anatomically near pelvis (122–124) probably related to their closeness to radiation fields or to platinum residue in urothelial tissue. Conversely, cases of secondary leukemia may be related to platinum-dependent alterations in the bone marrow (125). Together with accumulated psychological stress, such factors could influence the aging of the immune system in TC survivors.

CONCLUSIONS AND PERSPECTIVES

Cancer therapies are life-saving for countless patients but are also associated with side-effects (some long-term) on aging and on the immune system that may be responsible for multiple morbidities (13). Whilst platinum-based therapies are extremely efficacy for recurrent or metastatic TC, platinum is still detectable in the plasma of patients up to 20 years after treatment and it could have deleterious consequence on the organism (101–103). Moreover, also the psychological distress caused by challenges faced during the course of the disease are able to induce the onset of an early-aging phenotype and a decline of the immune system (14). TC survivors struggle with high rates of anxiety and PTSD (73–75) and with the effect of adverse events such as hypogonadism, metabolic disorder, and second malignancies (100). Thus, a better understanding of immunosenescence and of its molecular mechanisms is needed to improve therapeutic options and mitigate their late-effects on cancer patients. Features of senescence involving the adaptive immune response have been reported in TC survivors treated with three or more cycles of chemotherapy (58), however, the overall picture of the long-term effect of current TC management on the immune system is still incomplete. Other studies are needed to address how psychological stress caused by the diagnosis and treatment of a life-threatening disease could affect the immune system. Numerous other molecular aspects accelerating the aging process could also be studied in this cancer setting. A better comprehension of immunosenescence in the general population and of its causes and effects in cancer patients is desirable, hoping to shed the light to some events that could be improved to ameliorate the management of TC survivors. Further research is warranted to identify factors associated with immune aging, late complications and stress in TC survivors, and screening programs should be inserted into follow-up programs.

AUTHOR CONTRIBUTIONS

SP, UG, and MU conceptualized and designed the study. MU, SP, and GS drafted the manuscript. GR and LG supervised the project. PU, FF, AV, and GG contributed to the writing and critical discussion of molecular aspects. EM, TB, FR, and LG contributed to the writing and critical discussion of psychological aspects. UG, LR, CC, and GR contributed to the writing and critical discussion of TC medical aspects. All authors contributed to the article and approved the submitted version.

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