

A Case Report of Acute Lymphoblastic Leukaemia (ALL)/Lymphoblastic Lymphoma (LBL) Following the Second Dose of Comirnaty®: An Analysis of the Potential Pathogenic Mechanism Based on of the Existing Literature

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Case Report

A Case Report of Acute Lymphoblastic Leukaemia (ALL)/Lymphoblastic Lymphoma (LBL) Following the Second Dose of Comirnaty®: An Analysis of the Potential Pathogenic Mechanism Based on of the Existing Literature

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Abstract: In this report we describe the case of a healthy, young, athletic woman who developed acute lymphoblastic leukaemia (ALL)/lymphoblastic lymphoma (LBL) after receiving the second dose of the Pfizer/BioNTech modified mRNA (modRNA) COVID-19 genetic vaccine (marketed as Comirnaty®). The first dose of the genetic vaccine did not appear to illicit any noticeable side effects, but within 24 hours of the second dose the patient suffered widespread and intensifying bone pain, fever, vomiting, and general malaise. Due to the persistence of the symptoms, the patient underwent a series of tests and examinations including a full laboratory workup, a consult with a clinical immunologist and rheumatologist, a Positron Emission Tomography (PET) imaging, as well as an osteomedullary biopsy. These together led to a definitive diagnosis of ALL. A time interval of 16 weeks from the second vaccination to the diagnosis of cancer was noted. Several similar cases with identical pathology which developed after the modRNA COVID-19 vaccination, are described in case reports in the scientific literature. The massive and indiscriminate use of genetic vaccines to fight COVID-19 is raising serious concerns about their safety and about the technology platform as a whole for this purpose. Growing evidence is accumulating regarding the biodistribution and persistence of the modRNA which can reach, thanks to the lipid nanoparticles, a multitude of tissues and organs of the body, including the bone marrow and other blood-forming organs and tissues. Moreover, there is evidence that the modRNA vaccines display a particular tropism for the bone marrow, influencing the immune system at multiple levels and being able to trigger not only autoimmune-based pathologies, but also neoplastic mechanisms. The aim of this article is to assess, on the basis of the available scientific literature, the risk of developing haematopoietic cancers after modRNA vaccination, and to investigate the potential genetic mechanisms involved in the pathogenesis of disease.

Keywords: COVID-19 genetic vaccines; mRNA vaccines; adverse effects; lymphoblastic leukemia; lymphoblastic lymphoma

Introduction

Acute lymphoblastic leukaemia (ALL)/lymphoblastic lymphoma (LBL) is a clonal haematopoietic stem cell disorder of B or T cell origin, and the World Health Organization 2017 Classification System categorizes these disease entities under "Precursor Lymphoid Neoplasms" [1]. Several authors have expressed their concerns regarding the safety of mRNA vaccines against COVID-19 [2–10], which are technically prodrug gene therapies encased in lipid nano particles

(LNPs), rather than natural naked mRNA [11,12]. The LNPs allow for unfettered access through most tissues and organs including the brain and the bone marrow [13,14]. The mRNA is further modified (modRNA) by the substitution of all of the uridines for N1-methylpseudouridine (m1Ψ), in order to better stabilize the mRNA and also cloak it from the immune system [15].

In parallel to the rollout of the genetic vaccines, an increase in excess mortality is being reported in several countries worldwide [16,17]. According to a recent study performed in Japan, the age-adjusted death rates for leukaemia, breast, pancreatic, and lip/oral/pharyngeal cancers increased significantly in 2022 after a large portion of the Japanese population had received the third dose of the modRNA vaccine, as compared to 2020, the first year of the pandemic, when no mass global genetic vaccinations were given [18]. Likewise, a study aimed to estimate the excess mortality in Germany for the years 2020-2022, showed that in 2020, there were approximately 4,000 excess deaths, while in 2021 and 2022, there were approximately 34,000 and 66,000 excess deaths; respectively [19]. The authors conclude that something must have happened in spring 2021 that led to a sustained increase in mortality.

Dr. Ute Kruger, a prominent physician and researcher at Lunds University in Sweden, with 25 years of experience in pathology and oncology, has recently proposed a theory that the genetic vaccines may be causing aggressive tumours that she named “Turbo Cancers” [20].

Despite over 30 years of studying mRNA technology as gene therapy for the treatment of certain conditions including genetic defects such as inborn errors in metabolic genes and cancers, this technology was first applied as a means to generate an immune response against a target antigen and termed a “genetic vaccine” designed to vaccinate healthy individuals against SARS-CoV-2, during the recent pandemic. Inoculation commenced early on, spanning all age groups, including vulnerable individuals and pregnant women, despite there being no long-term safety data and no data at all on genotoxicity or cancer [4]. As relayed above, preliminary studies on carcinogenicity and genotoxicity were not conducted, and the randomized trial study of the Pfizer/BioNTech vaccine was prematurely halted after approximately 6 months, offering the placebo group the chance to vaccinate [21,22], thus losing any opportunity to understand the medium- to long-term repercussions, particularly concerning carcinogenesis. This, despite the fact that gene therapy has long been known to bear an oncogenic risk due to the phenomenon of insertional mutagenesis [23–25].

Numerous studies report the occurrence of lymphadenopathies, often with suspicious characteristics in draining lymph nodes after vaccine administration, indicating significant stress on the immune system. A study on 951 consecutive patients, subjected to PET-CT, revealed metabolic activity in axillary and supra-clavicular lymph nodes in 45.6% of vaccinated patients, especially after the second dose (53.9%) [26]. In 17 vaccinated patients (5.1%), “hot” lymph nodes reflected malignant lymph node disease, in 266 patients (80.1%) the “hot” lymph nodes were benign and vaccine-associated, while in 49 patients (14.8%), the nature of the lymph nodes was uncertain [26].

It is well-established that both natural and vaccine-derived spike proteins are toxic [27], but the latter is more persistent due to a double proline that confers greater stability. Additionally, the synthetic pseudouridines contained in the modRNA have shown mitochondrial toxicity in other applications, as warned of by the genetic vaccine developers Karikó and Sahin [28]. Recently it has been found that this modification also causes frame shift mutations during translation that cause the production of a multitude of peptide products to be differentially expressed between individuals [29]. This obviously poses serious safety concerns as only a single antigen was supposed to be encoded by the modRNA, not many undefined peptides with unknown antigenic and auto-immune potential. The encapsulation of the modRNA in LNPs not only allows systemic diffusion [30], but also presents intrinsic cytotoxicity, a source of significant concern [31,32]. Furthermore, the LNPs display a distribution beyond the injection site, to a wide variety of tissues, including the bone marrow [4,13,14], and this could affect haematopoiesis.

Case Report

The case involves a 38-year-old woman who received the second dose of Comirnaty® in July 2021. Before the symptoms started, she constantly had a healthy lifestyle and participated in athletic

activities like pole dancing and callisthenics. There is no significant family or pathophysiological history. Consistent clinical and laboratory assessments, carried out in parallel with her athletic activities (in 2016, 2017, 2019 - most recent on April 13, 2021), did not yield any noteworthy findings.

Recent Medical History:

The first dose of Comirnaty®, administered on June 20, 2021, did not induce notable symptoms. On the morning of July 20, 2021, the day after the administration of the second dose of Comirnaty® (both administrations occurred at public facilities), the patient experienced significant discomfort. She woke up with a locked neck and jaw, tinnitus, nausea, diffuse pain, low-grade fever, headache, and sweating. Symptoms worsened in the following days, accompanied by insomnia, hypersensitivity to temperature changes, and noise. The patient consulted her primary care physician and took ketoprofen lysine salt 80 mg (OKI®), and paracetamol 500 mg (Tachipirina®), resulting in only a mild and transient reduction in symptoms. Due to persistent symptoms, on August 6, 2021, haematological tests were performed, revealing altered blood counts with neutropenia and lymphocytosis: WBC 5230/mm³ (normal range: 5000-10000/mm³), neutrophils 1400/μL (normal range: 1900-8000/μL), equivalent to 26.8% (normal range: 40-74%), lymphocytes 3390/μL, equivalent to 64.8% (normal range: 19-48%), elevated erythrocyte sedimentation rate (ESR) at 59 mm/hour (normal female <50 years-old range: ≤ 20 mm/hour), transferrin 233 mg/dL (normal female range: 250–380 mg/dL). Hemoglobin, platelets, liver and kidney function indices were within normal ranges. As the subjective symptoms continued to be increasingly disabling, further examinations were conducted: (i) On September 8, 2021 a laboratory check revealed mild anaemia (Hb 10.8 g/dL, normal range: 12.3-15.3 g/dL), mean cell volume (MCV) 103.6 fL (normal range: 80-100 fL), neutrophils 990/μL (normal range: 1900-8000/μL), equivalent to 22.9% (normal range: 40-74%), increased lymphocytosis (lymphocytes 70.4%, normal range: 19-48%), and ESR 66 mm/hour (normal female <50 years-old range: ≤ 20 mm/hour). Other parameters, including C-reactive protein, complement factors, rheumatoid factor, thyroid-related antibodies, were within normal limits; on (ii) October 1, 2021 the laboratory analyses confirmed anaemia (Hb: 10.4 g/dL, normal range: 12.3-15.3 g/dL), neutrophils 1370/μL (normal range: 1900-8000/μL), equivalent to 29% (normal range: 40-74%), persistent lymphocytosis (lymphocytes 65.8%, normal range: 19-48%), mean cell volume (MCV) 103.4 fL (normal range: 80-100 fL) and an elevated ESR 96 mm/hour (normal female <50 years-old range: ≤ 20 mm/hour). Homocysteine, creatine kinase, and C-reactive protein were normal. Serological tests for hepatitis, rubella, Epstein-Barr, Cytomegalovirus, Treponema, Toxoplasma, as well as autoantibodies (ANA, ANCA, ENA, ADNA, and anti-citrulline) were all negative; on (iii) October 16, 2021 the ESR was 118 mm/hour (normal female <50 years-old range: ≤ 20 mm/hour). The ESR increased progressively from August 6 to October 16 and was as follows: 59-66-96-118 mm/hour. A rheumatological examination on October 22, 2021, suggested post-vaccination inflammation following the second dose of Comirnaty® (July 19, 2021), with symptoms including arthromyalgia, headache, low-grade fever, night sweats, and an ESR of 118 mm/hour. The patient was diagnosed with polymyalgia rheumatica (PMR)/vasculitis of large vessels post-vaccination. She was recommended to undergo a PET scan with a big vessel wall uptake analysis, and steroid therapy afterward. PET scan on November 15, 2021, revealed intense uptake in the medullary component of the entire axial and appendicular skeleton and diffuse increased uptake in the spleen. Suspecting lymphoproliferative pathology, urgent haematological consultation was initiated, leading to an haematological examination, bone marrow aspiration, and biopsy on December 1, 2021.

Clinical Examination and Diagnosis:

Clinical examination revealed no superficial lymphadenopathy, and the abdomen and chest were normal. The patient experienced significant diffuse pain and intense sweating from early October, persisting until the beginning of chemotherapy, with a brief interval following corticosteroid therapy. Blood analysis on November 29 showed Hb 9.1 g/dL, WBC 4030/mm³, neutrophils 1810/mm³, lymphocytes 2180/mm³, circulating atypical lymphoid elements, rare immature myeloid elements, C-reactive protein 2.18 mg/dL (normal range: 0.3-1.0 mg/dL), beta-2 microglobulin (B2M)

level of 2.7 mg/dL (normal range: <0.2 mg/dL). Bone marrow aspirate and biopsy revealed near-total replacement of haematopoietic components by a massive and widespread infiltrate of blast-like elements (approximately 95% of nucleated cells), with irregular or cleaved nuclei characterized by the following immunophenotypic profile: TdT(+), CD34(+), CD79a(+), PAX5(+), CD20(-/+), CD10(+), MYC(-/+), CD3(-), CD5(-), Cyclin D1(-), CD23(-), pg53(-), MPO(-), residual haematopoietic component represented by scattered erythroblasts and rare dystrophic megakaryocytes. The immunophenotypic profile indicated a precursor B-lymphoid neoplasm, specifically B-lymphoblastic leukaemia/lymphoma (according to the WHO classification). The patient initiated the prescribed chemotherapy protocol, achieved complete remission, and is currently undergoing maintenance therapy.

Discussion

An experimental COVID-19 genetic vaccine animal study involving 28 BALB/c mice, aimed at investigating the pathogenesis of myocarditis following modRNA COVID-19 vaccination, unexpectedly provided crucial insights into the carcinogenicity of these products [33]. Fourteen animals received saline solution, while the remaining were intravenously infused with the modRNA vaccine (BNT162b2). Surprisingly, two days after the booster vaccination (16 days after the first), one of the mice experienced spontaneous death with marked organomegaly and widespread malignant infiltration of the heart, lungs, liver, kidneys, and spleen, consistent with B-cell lymphoblastic lymphoma. This was noted at just 14 weeks of age. It is noteworthy, that the information sheet for the ENVIGO BALB/c model reports a zero incidence of background rates of lymphatic leukaemia [34]. The authors state that while a definitive causal relationship between the modRNA vaccine and the observed lymphoma in the animal cannot be established, the temporal sequence of events suggests its involvement in this rare haematologic neoplasm.

Several papers, mostly “Case Reports” describe malignancies that developed in close temporal relationship with modRNA COVID-19 vaccinations. A total of 28 studies were identified, with 26 focusing on haemato-lymphoproliferative disorders. Among the case reports, there are 9 cases of B-cell lymphoproliferative disorders, 11 involving the T-cell line, 6 affecting the myeloid line, and 2 cases related to the onset of solid tumours. A summary is presented in Tables 1, 2 and 3, detailing cases involving the lymphoid series categorized by B and T phenotypes, and the myeloid series, respectively.

Table 1. Lymphoproliferative disorders following COVID-19 vaccination with a B-phenotype (DLBCL: Diffuse large B-cell lymphoma; MZL: Marginal zone B-cell lymphoma; B-ALL: Acute lymphoblastic leukaemia B; IVLBCL: Intravascular large B-cell lymphoma; *: Patient in remission for two years after treatment for non-Hodgkin’s lymphoma).

| Case n° | Sex/Age (ref.) | Time elapsed from vaccination to onset of symptoms | Histology | Vaccine type | Site |
|---------|----------------|--|-----------|--|---------------------------|
| 1 | F/58 [35] | 1 week | DLBCL | Pfizer/BioNTech (2 nd dose) | Left cervical area |
| 2 | F/80 [36] | 1 day | MZL | Pfizer/BioNTech (1 st dose) | Right temporal lobe |
| 3 | M/51 [37] | 7 days | DLBCL | Astra Zeneca (1 st dose) | Mediastinum |
| 4 | M/67 [38] | 2 weeks | DLBCL | Pfizer/BioNTech (2 nd dose) | Axilla |
| 5 | F/80 [38] | 2 days | DLBCL | Pfizer/BioNTech (2 nd dose) | Axilla |
| 6 | F/49 [39] | 2 days | B-ALL | Pfizer/BioNTech (dose n.s.) | Bone marrow |
| 7 | F/47* [39] | Few days | B-ALL | Pfizer/BioNTech (dose n.s.) | Bone marrow |
| 8 | F/43 [40] | Few days | B-ALL | Moderna (dose n.s.) | Bone marrow |
| 9 | F/61 [41] | Few weeks | IVLBCL | Pfizer/BioNTech (2 nd dose) | Multi-organ blood vessels |

Table 2. Lymphoproliferative disorders following COVID-19 vaccination with a T-phenotype (ENKTCL: Extranodal malignant non-Hodgkin lymphoma with T/NK cells; AITL: Angioimmunoblastic T-cell lymphoma; ENKL: Extranodal NK/T-cell lymphoma, nasal type; SPTCL: Panniculitis-like T-cell lymphoma; ALCL: Anaplastic large cell lymphoma; CTCL: Cutaneous T-cell lymphoma; T-ALL NK= T Cell lymphoblastic leukemia with NK phenotype).

| Case n° | Sex/Age (ref.) | Time elapsed from vaccination to onset of symptoms | Histology | Vaccine type | Site |
|---------|----------------|--|-----------|--|----------------------------------|
| 1 | M/53 [35] | 3 days | ENKTCL | Pfizer/BioNTech (1 st dose) | Oral cavity |
| 2 | M/66 [42] | 1 week | AITL | Pfizer/BioNTech (2 nd dose) | Lymph nodes |
| 3 | M/73 [43] | 3 months | ENKL | Pfizer/BioNTech (2 nd dose) | Injection site |
| 4 | F/28 [44] | 3 days | SPTCL | Janssen Pharmaceuticals | Injection site |
| 5 | M/45 [45] | 3 days | SPTCL | Moderna (dose n.s.) | Periumbilical region |
| 6 | M/76 [46] | 10 days | ALCL | Moderna (3 rd dose) | Injection site |
| 7 | M/60 [47] | 4 weeks | CTCL | Astra Zeneca (dose n.s.) | Occipital area |
| 8 | F/73 [47] | 10 days | CTCL | Astra Zeneca (dose n.s.) | Skin |
| 9 | M/66 [48] | 10 days | ALCL | Pfizer/BioNTech (3 rd dose) | Cervical an axillary lymph nodes |
| 10 | M/55 [49] | 2 days | T-ALL NK | mRNA (brand & dose n.s.) | Neck lymph node & bone marrow |
| 11 | M/79 [50] | 3 days | CTCL | Moderna (3 rd dose) | Injection site |

Table 3. Myeloproliferative disorders following modRNA COVID-19 vaccination (AML: Acute myeloid leukaemia; CMML: Chronic myelomonocytic leukaemia; *: Return of AML into remission after allogeneic transplant 14 years earlier).

| Case n° | Sex/Age (ref.) | Time elapsed from vaccination to onset of symptoms | Histology | Vaccine type | Site |
|---------|----------------|--|-----------|--|-------------|
| 1 | F/67 [39] | 2 months | AML* | Pfizer/BioNTech | Bone marrow |
| 2 | M/60 [51] | 1 month | AML | Pfizer/BioNTech (4 th dose) | Bone marrow |
| 3 | M/61 [51] | 1 month | AML | Pfizer/BioNTech (3 rd dose) | Bone marrow |
| 4 | M/72 [51] | 5 weeks | AML | Pfizer/BioNTech (5 th dose) | Bone marrow |
| 5 | F/28 [51] | 4 weeks | AML | Pfizer/BioNTech (2 nd dose) | Bone marrow |
| 6 | F/74 [46] | 4 days | CMML | Janssen Pharmaceuticals | Bone marrow |

In the overwhelming majority of cases, there is a *de novo* onset of proliferative disorders affecting the lymphoid lineage, encompassing both B and T phenotypes. The Pfizer/BioNTech vaccine appears to be the most implicated (16 cases). The onset of symptoms following vaccine inoculation has generally been very brief, even within a few days, as seen for instance in the cases reported by Kreher et al., Ukishima et al. and Panou et al. [44,45,47]. In one case, acute lymphoblastic leukemia occurred in a 47-year-old woman who had been in remission for two years from a B-cell lymphoma [39]. Two cases of T-cell lymphomas exhibited a recurrence of previously well-controlled conditions (mucosis fungoides and lymphomatoid papulosis) [47]. Notably, in lymphoma cases, four cases showed onset at the inoculation site [43,44,46,50], and three cases manifested in draining lymph nodes (axillary and lateral cervical) [35,38,48]. An interesting case involves angioimmunoblastic T-cell lymphoma, where rapid progression was observed after the booster dose [42]. The patient, previously vaccinated with 2 doses of Comirnaty® 5 and 6 months earlier, had developed a rare form of lymphoma and underwent a staging PET/CT on September 8. Fourteen days later, the patient received a booster dose of the same vaccine in preparation for chemotherapy, and repeated a PET/CT on September 30. The initial PET/CT revealed the presence of hypermetabolic lymph nodes mainly in the supra-clavicular, cervical, and left axillary regions, as well as restricted gastro-intestinal hypermetabolic lesions. However, the second PET/CT revealed a dramatic increase in nodal and gastro-intestinal hypermetabolic lesions, as well as asymmetrical metabolic progression in the cervical, supra-clavicular and axillary areas.

Regarding solid tumours that developed soon after receiving the modRNA COVID-19 vaccination, two cases were reported: one involved a 64-year-old woman who had a significant

history of previously excised cutaneous melanoma reoccurring to the breast [52], and the other involved an aggressive sarcoma that developed at the injection site shortly after the second dose of Moderna [53].

Potential Carcinogenic Mechanisms Induced by COVID-19 modRNA Vaccines

Several mechanisms have been proposed by which the current modRNA COVID-19 vaccines may exert a carcinogenic effect, inducing both *de novo* tumour formation and the recurrence of neoplastic diseases in remission. It is also evident, that the genetic material and the vaccine derived spike protein have a significant impact on the immune system and may compromise immune surveillance against altered cellular clones in a manner that could lead to cancer.

The main alterations induced by modRNA COVID-19 vaccines reported in literature, that may have an oncogenic outcome are listed below:

- (i) The alteration of the inhibitory immune checkpoint mediated by the programmed cell death protein 1 (PD-1, CD279), which is primarily found on T-cells, mature B-cells, and other immune cells. The overexpression of the programmed death-ligand 1 (PD-L1), observed in vaccinated individuals, leads to T-cell immunosuppression, impairing cancer surveillance [54].
- (ii) The interaction between the S2 subunit of the spike protein and the oncosuppressor proteins p53, BRCA1, and BRCA2, which regulate downstream genes in response to numerous cellular stress and play a crucial role in preventing cancer [55].
- (iii) The impairment in type I interferon (IFN) signalling, which play essential roles in inflammation, immunomodulation, tumour cell recognition, and T-cell responses [56].
Differential gene expression analysis of peripheral dendritic cells revealed dramatic upregulation of type I and type II IFNs in COVID-19 patients, but not in vaccinees. All this supports the possibility that COVID-19 genetic vaccines actively suppress the production of type I IFN which play a fundamental role in the immune reaction in response to multiple stressors, especially viral infections and tumours. In the presence of a viral infection, the production of type I IFN drastically increases and IFN- α , released in the lymph nodes, induces B-cells to differentiate into plasmablasts and subsequently, thanks to IL6, to evolve into antibody-secreting plasma cells. As regards the anti-tumour action of IFNs, this occurs through both direct and indirect mechanisms. Direct effects include cell cycle arrest, induction of cell differentiation, initiation of apoptosis, and activation of natural killer and CD8⁺ T-cells. The indirect anti-tumour effects are mainly due to the activation of transcription factors which improve the expression of at least 150 genes also involved in apoptosis.
- (iv) Increased Transforming Growth Factor Beta (TGF- β) Production. The interaction between the SARS-CoV-2 spike protein and the angiotensin-converting enzyme 2 (ACE2) induces TGF- β release by cells such as alveolar and tissue macrophages, lung epithelial cells, endothelial cells and B lymphocytes, promoting epithelial-mesenchymal transition (EMT) [57]. This process could explain the particular rapidity of onset and evolution of tumour forms arising following the administration of the COVID-19 genetic vaccines. In fact, the TGF- β is a growth factor capable of inducing in already differentiated cells a “regression” towards the mesenchymal state (a state typical of the early stages of embryonic life), with the ability to metastasize and greater biological aggressiveness.
- (v) The presence of LNP-encapsulated DNA contamination originating from residual plasmid DNA from DNA plasmids used during the manufacturing process of the Pfizer/BioNTech and Moderna modRNA genetic vaccines [58,59]. The residual DNA detected in the modRNA

genetic vaccines is high in copy number and contains elements such as: functional promoters, open reading frames (ORFs), origins of replication and nuclear targeting sequences [59]. In the case of the Pfizer/BioNTech genetic vaccine, such plasmids have been engineered with a mammalian SV40 promoter-enhancer-*ori* from the oncogenic virus Simian Virus 40 (SV40) along with a nuclear targeting sequence (NTS) [58,59]. This human compatible promoter is not required for the expression of these plasmids in the *E. coli* bacterial expression system and its presence is highly unusual as it poses a significant oncogenic risk that is not needed for the plasmid's stated purpose. The FDA has guidance for plasmid DNA-based genetic vaccines and while the modRNA are not defined as DNA based-vaccines, the contaminating plasmids' design is consistent with this application and it is expected that portions of the contaminating plasmid DNA with eukaryotic promoters and enhancers will pose the same risks of insertional mutagenesis. FDA advises the following: *"Plasmid biodistribution, persistence and integration studies were initially recommended to examine whether subjects in DNA vaccine trials were at heightened risk from the long-term expression of the encoded antigen, either at the site of injection or an ectopic site, and/or plasmid integration. Theoretical concerns regarding DNA integration include the risk of tumorigenesis if insertion reduces the activity of a tumor suppressor or increases the activity of an oncogene. In addition, DNA integration may result in chromosomal instability through the induction of chromosomal breaks or rearrangements."* [60]. Additionally, the presence of the contaminating plasmids is far above the regulated limits for naked DNA contamination on vaccines [58,59]. As recently reported by Cancer Geneticist Prof. Buckhaults [61] and by Toxicologist and Molecular Biologist Janci Lindsay, Ph.D. [62] before the South Carolina Senate Medical Affairs Ad-Hoc Committee, these are extremely serious and unexplainable contaminants of the Pfizer/BioNTech modRNA vaccines, because they increase the likelihood that these contaminating sequences from this oncogenic virus as well as other sequences contained within the plasmids and encapsulated within the LNPs, will integrate into the DNA of the vaccinees with consequences that are difficult to predict. Insertional mutagenesis is often leading to cancer, and in fact, gene therapy has long been known to bear an oncogenic risk as recognized by the FDA in their guidance on plasmid DNA vaccines [60], and the previous studies cited [23–25]. According to Buckhaults, the urgency of the pandemic crisis induced the pharmaceutical companies to take some "shortcuts", using bacteria for the mass production of the modRNA vaccines. The SV40 DNA sequences derive from a plasmid engineered for the modRNA production in bacteria, specifically modified to include the *SPIKE* gene. Pfizer/BioNTech tried to solve the problem by adding the enzyme deoxyribonuclease to chop the plasmid into millions of small fragments. However, according to Prof. Buckhaults, this actually increased the risks because the more fragments there are, the more likely it is that one of them will fit into the genome and interfere with crucial genes. Prof. Buckhaults and Dr. Lindsay expressed their concern about the theoretical, but very real risk of future cancer in some people, depending on where foreign pieces of DNA integrate in the genome, potentially disrupting suppressor genes or activating oncogenes. In fact, as relayed earlier the SV40 virus is a known oncogenic virus when intact [63,64]. There is also the additional potential for the modRNA to be reverse transcribed to DNA through the reverse transcriptase activity of LINE-1, as previously demonstrated by Aldén et al., especially in tissues such as the testes and ovaries as well as the bone marrow that are rich in this transcription factor [59,65].

- (vi) The role of the immunoglobulin subtype IgG4 in cancer immune evasion. Wang et al. found that IgG4-containing B lymphocytes and IgG4 concentration were significantly increased in cancer tissues, as well as in the serum of patients with cancer [66]. Both were positively correlated with worse prognoses and increased cancer malignancy. Previous works reported that IgG4 was generated locally in melanoma, playing an important role in removing the tumour from the control of the immune system and therefore facilitating its development [67,68]. Increased production of IgG4 is normally associated with prolonged exposure to antigens, and their interaction with antibodies of the IgG and IgE classes through their Fc domains has been reported [69]. IgG4 is in fact endowed with a dual role, as it can suppress or stop inflammation by competing with inflammatory IgE for binding to the antigen, in the case of allergies and infections from helminths and filarial parasites or, on the contrary, IgG4 can lead to serious autoimmune [70] and tumour diseases, playing an essential role in the “immune evasion” of cancer cells. Recent studies indicate that repeated modRNA vaccinations against COVID-19 shift the antibody response towards the IgG4 subclass with a decrease in FcγR-dependent effector activity and an increased mortality in case of COVID-19 infection [71–73]. In cohorts of healthy healthcare workers, it was demonstrated that several months after the second dose the SARS-CoV-2-specific antibodies were increasingly composed of non-inflammatory IgG4, which were further enhanced by a third modRNA vaccination and/or by infections of SARS-CoV-2 variants [72]. IgG4 antibodies, among all spike-specific IgG antibodies, increased on average from 0.04% shortly after the second vaccination, to almost 20% (19.27%) after the third vaccination [73]. In conclusion, the increase in IgG4 following repeated administration of modRNA vaccines is undoubted and this generates serious concerns regarding the involvement of IgG4 in the “immune evasion” of cancer cells.
- (vii) The incorporation of m1Ψ into the modRNA of the genetic vaccines causes ribosomal frame-shifting during translation, which can lead to the production of numerous peptide products that are expressed differently in each individual [29]. Given that these unidentified peptides may have unknown antigenic and auto-immune potential, they pose a serious risk for carcinogenesis that should be deeply investigated.

Conclusions

The development and widespread use of modRNA vaccines have raised significant concerns globally, leading to adverse events and complications in both healthy individuals and those with pre-existing conditions. Reports of increased cases of a variety of cancers [18], including highly aggressive cancers, termed “Turbo Cancer” [20] and the unexpected recurrence of cancers after decades of remission, have been independently noted by oncology experts and researchers worldwide, with several publications supporting these observations [35–51]. Understanding the mechanisms behind the carcinogenic effects of the modRNA COVID-19 vaccines is crucial. Immune system alterations, notably T-cell suppression, the decreased production of IFN type I, interference with oncosuppressor genes and proteins, inhibition of DNA repair mechanisms, and overexpression of cell death proteins in T-cells, are key factors facilitating neoplastic/oncogenic transformation [54–56]. Increased TGF-β production, promoting EMT, may explain the aggressive nature of observed tumours [57]. Additionally, the detection of hazardous and unexplainable contamination of the modRNA vaccines with plasmid DNA sequences deriving from the manufacturing process needs to be investigated. What is the purpose for the addition of a mammalian promoter and nuclear targeting sequence from the SV40 oncovirus in the plasmid used in the manufacturing process of the Pfizer/BioNTech genetic vaccine, supposedly meant to only be used to grow copies in bacteria, where a mammalian promoter

and obviously a nuclear targeting sequence, is not needed? Such very concerning issues must be appropriately addressed by the global safety and regulatory agencies. Just as the risk of developing myocarditis and pericarditis following modRNA COVID-19 vaccination has been recently acknowledged [74], similar attention should be paid to assess the potential risk of developing cancer associated with the genetic vaccines. Since the development of modRNA vaccines is also already in motion for other diseases and this platform is planned to replace the existing traditional vaccine platform for the childhood vaccines, the carcinogenic risk of these technologies, which has been long known to the gene therapy platform, especially for leukaemias and lymphomas, represents a field of research that cannot be ignored, given that the fundamental principle of medicine, which is “*primum non nocere*”. It is therefore crucial to perform extensive pharmacodynamic, pharmacokinetic and genotoxicity evaluations, as well as population-based observational studies, in order to assess the potential carcinogenic risk posed by the genetic vaccines and to understand its pathogenic mechanism.

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