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Original research

The Effect of Immunizing with Neural Derived Peptides on the Expression of Inflammatory Genes Depends on the Severity of Spinal Cord Injury

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ABSTRACT

Introduction: Spinal cord injury (SCI) triggers an inflammatory response that exacerbates tissue damage and limits neuronal regeneration. This response involves the overexpression of inflammatory genes associated with oxidative stress, apoptosis, and demyelination. A promising neuroprotective strategy is immunization with neural-modified peptides (INMP), such as A91 and Cop-1, derived from myelin basic protein. These peptides induce a regulatory immune response via Th2-type T lymphocytes, promoting an anti-inflammatory environment. **Methods:** A severe contusion model of SCI was used in rats. Following injury, animals were immunized with either A91 or Cop-1. Spinal cord tissue was collected seven days post-injury for transcriptomic analysis using microarray technology. Gene expression profiles were compared to a non-immunized control group (PBS). **Results:** Both treatments led to a general reduction in the expression of inflammatory genes. However, only A91 immunization resulted in a statistically significant downregulation of eleven key genes: *Bmp2, Casp1, Casp3, Ccl2, Cebpb, Cish, Socs2, Socs3, Il1rap, Tgfb3,* and *Tnfs11*. These findings are consistent with previous studies from our group, which suggest that the neuroprotective effects of INMPs are less evident in cases of severe SCI. **Conclusion:** Immunization with INMPs modulates the inflammatory response following severe SCI. A91 produced a more pronounced effect than Cop-1, suggesting greater therapeutic potential. These results indicate that gene expression responses to INMPs may vary depending on injury severity, and further research is required to optimize therapeutic strategies.

Key words: gene expression; neural-derived peptides; spinal cord injury.

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RESUMEN

Introducción: La lesión de la médula espinal (LME) activa una respuesta inflamatoria que agrava el daño tisular y limita la regeneración neuronal. Esta respuesta implica la sobreexpresión de genes inflamatorios, relacionados con procesos como estrés oxidativo, apoptosis y desmielinización. Una estrategia neuroprotectora es la inmunización con péptidos neurales modificados (INMP), como A91 y Cop-1, derivados de la proteína básica de mielina. Estos péptidos inducen una respuesta inmune reguladora mediante linfocitos T tipo Th2, promoviendo un entorno antiinflamatorio. **Metodología:** Se utilizó un modelo de contusión medular severa en ratas. Tras la lesión, los animales fueron inmunizados con A91 o Cop-1. A los siete días post-lesión se obtuvo la médula espinal para análisis transcriptómico mediante microarreglos. Los perfiles de expresión génica se compararon con un grupo control no inmunizado (PBS). **Resultados:** Ambos tratamientos redujeron la expresión general de genes inflamatorios. Sin embargo, solo la inmunización con A91 mostró una disminución estadísticamente significativa en once genes clave: *Bmp2, Casp1, Casp3, Ccl2, Cebpb, Cish, Socs2, Socs3, Il1rap, Tgfb3* y *Tnfs11*. Estos hallazgos coinciden con estudios previos de nuestro grupo, que indican que los efectos neuroprotectores de los INMP son menos evidentes en casos de LME severa. **Conclusión:** La inmunización con INMP modula la respuesta inflamatoria tras LME severa. A91 mostró un efecto más significativo que Cop-1, lo que sugiere un mayor potencial terapéutico. Estos resultados sugieren que la respuesta génica a los INMP varía según la gravedad de la lesión, y se requiere mayor investigación para optimizar las estrategias terapéuticas.

Palabras clave: expresión génica; péptidos de origen neural; lesión medular.

INTRODUCTION

Following spinal cord injury (SCI), several autodestructive mechanisms have been observed. These include significant calcium influx into the cellular compartment, neural fiber damage, metabolic disturbances, destruction of microvessels, and breakdown of the blood-medullary barrier. The latter results in the recruitment of immune cells at the injury site (neutrophils, hematogenous macrophages, and T lymphocytes) and the activation of resident microglia, which triggers an inflammatory reaction at the damaged area, leading to an increased inflammatory response. This inflammatory process is mediated by different cells and proinflammatory cytokines, which exacerbate lipid peroxidation, free radical production, and demyelination, ultimately resulting in extensive secondary tissue damage.[1,2] Furthermore, the exacerbated inflammatory response can trigger a pathological autoreactive reaction, primarily mediated by the activation of T lymphocytes. If these lymphocytes differentiate into a Th1 phenotype (proinflammatory), they contribute to increased demyelination and expansion of the injury. However, if the response is directed toward a Th2 phenotype, the balance Th1/Th2 could regulate secondary damage by developing a neuroprotective microenvironment.[3–5]

The immune response has been demonstrated to play a pivotal role in the pathophysiology of secondary injury.[6] Recently, it has been demonstrated that modulating rather than inhibiting the immune response is beneficial and promotes neurological recovery after SCI.[7,8] Protective autoimmunity (PA) is an innovative strategy based on immune response modulation.[5,9–11] This approach is enhanced by immunization with non-encephalitogenic neural-modified peptides (INMP) such as A91 or Cop-1[3,12] A91 is a myelin basic protein (MBP)-derived peptide (sequence 87-99), obtained by replacing the lysine residue at position 91 with alanine.[12–14] On the other hand, Cop-1 is a random polypeptide synthesized from four amino acids (L-tyrosine, L-glutamic acid, L-alanine, and L-lysine), with an average molar fraction of 0.141, 0.427, 0.095, and 0.0338, respectively.[15,16]

Despite promising results, the precise mechanisms by which PA exerts its neuroprotective effects remain unclear, and many aspects have yet to be elucidated. Gene expression analysis may provide valuable insights into these mechanisms, as gene regulation can influence cellular function over both short and extended periods. Based on our previous studies, the neuroprotective effects of A91 and Cop-1 were found to be limited in cases of severe compared to moderate SCI, we aimed to investigate gene expression changes seven days after severe SCI, following immunization with A91 or Cop-1. Gene expression profiling was performed using microarray analysis to identify novel therapeutic targets associated with INMP in the context of severe spinal cord injury.

MATERIALS AND METHODS

Study Design

The sample size for this experiment was calculated using an alpha level of 0.05 and a beta of 0.20. Sixteen rats were subjected to severe spinal cord contusion and were randomly assigned to four groups (GraphPad QuickCalcs: http://www.graphpad.com/quickcalcs/): (1) non-immunized rats receiving PBS (n = 4), (2) rats immunized with A91 peptide (n = 4), (3) rats immunized with Cop-1 (n = 4), and (4) Sham-operated rats (n = 4), which were used to normalize gene expression values across all experimental groups. Seven days post-injury, all animals were euthanized, and spinal cord tissue was collected for microarray analysis of inflammation-related gene expression.

Animals

Adult female Fischer 344 rats (F344; 13–14 weeks old, 200–230 g; *n* = 12) were used in three independent experiments. Animals were obtained from Proyecto Camina A.C. and housed according to NIH guidelines for the care and use of laboratory animals. All procedures were approved by the Animal Bioethics and Welfare Committee (Protocol ID: 57204; CSNBTBIBAJ 090812960) and conducted in compliance with the Mexican Official Norm for Laboratory Animal Care (NOM-062-ZOO-1999).

Spinal Cord Injury

Rats were anesthetized with intramuscular ketamine (100 mg/kg; Probiomed, Mexico City) and xylazine (10 mg/kg; Fort Dodge Laboratories, IA, USA). A T9 laminectomy was performed to expose the spinal cord, and a 10 g rod was dropped from a height of 50 mm onto the exposed cord using the New York University (NYU) Impactor to induce a severe SCI.[17,18] After surgery, muscles and skin were sutured in layers. Animals were kept in a temperature-controlled environment at 23°C for the first 7 days post-injury. Manual bladder expression was performed twice daily. Antibiotics (enrofloxacin, 64 mg/kg/day; Marvel, Mexico City) and analgesics were administered daily to prevent infections and minimize pain.

Active Immunization

Sixty minutes after injury, rats were immunized subcutaneously at the base of the tail with a single dose of 150 µg of either A91, Cop-1, or 0.15 M phosphate-buffered saline (PBS), each emulsified in an equal volume of complete Freund's adjuvant (CFA) containing 0.5 mg/mL *Mycobacterium tuberculosis*. A91 (purity >95%) was obtained from Invitrogen Life Technologies (San Diego, CA), and Cop-1 was purchased from Sigma (St. Louis, MO).

Microarray Analysis

Gene expression analysis was focused on 90 inflammation-related genes. Seven days post-injury, a 3 cm spinal cord segment centered at the injury site was collected. Total RNA was extracted using the TRIzol-chloroform method (Sigma-Aldrich), followed by purification using the SuperArrays RT-QPCR grade RNA isolation protocol. RNA concentration and purity were assessed via UV spectrophotometry. Only samples with an A260:A280 ratio of ~2.0 and intact ribosomal bands (28S and 18S) on agarose gel electrophoresis were used.

Complementary RNA (cRNA) was synthesized from 2 µg of total RNA using the TrueLabeling-AMP™ 2.0 Kit (Oligo GEArray®, SuperArrays), incorporating biotin-6-UTP. cRNA was purified using the ArrayGrade™ Cleanup Kit and hybridized to nylon membrane arrays. Each array was performed in quadruplicate. Images were acquired using a cooled CCD camera, and data were analyzed with the SABiosciences GEArray® Expression Analysis Suite. Ribosomal protein L32 and lactate dehydrogenase A (LDHA) were used as internal controls. Expression levels were reported in arbitrary units after normalization. Gene expression from injured tissue was compared to sham-operated controls. A change greater than a 1-fold increase or a decrease of more than 50% was considered significant.

Data Analysis

ImageJ software was used to quantify signal intensity and density (IntDen) for each microarray spot. The same area was selected for all samples using the "rectangle" tool. Expression data from all 90 genes across 15 arrays (three per group) were analyzed. Delta 1 values were calculated for each gene using LDHA (lactate dehydrogenase A) as a normalization control, and Delta 2 values were derived by comparing results to the Sham group.

Statistical Analysis

Statistical significance was determined using the Kruskal–Wallis test or the Mann–Whitney U test. A *p* value ≤ 0.05 was considered statistically significant.

RESULTS

To elucidate the molecular mechanisms underlying the neuroprotective effects of A91 and Cop-1, we analyzed the gene expression profiles induced by these synthetic peptides using microarray assays. A broad range of differentially expressed genes was observed in the microarray clustergram across the A91, Cop-1, PBS, and Sham groups (Figure 1).

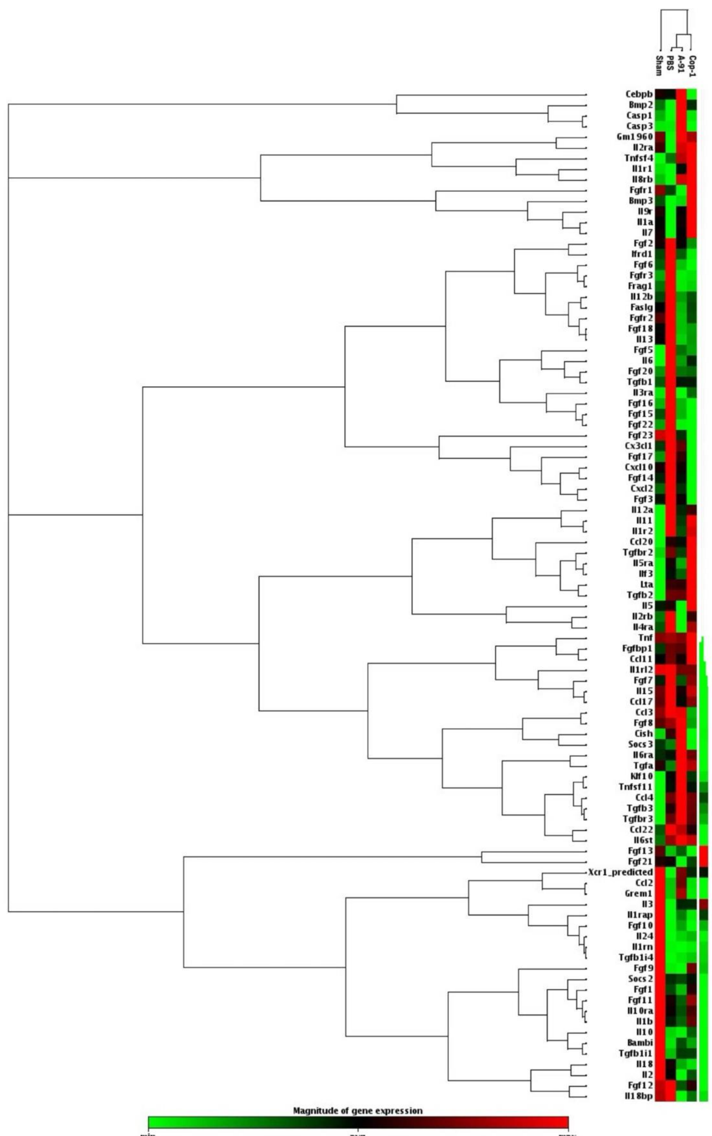

FIGURE 1. Clustergram of inflammatory gene expression following severe SCI in rats immunized with A91 or Cop-1. Colors indicate the relative magnitude of gene expression changes. Several inflammatory genes exhibited differential expression in both the A91 and Cop-1 treatment groups.

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Gene expression changes were systematically analyzed and compared across all experimental groups in the study, with Delta 2 values represented relative to the Sham group. Table 1 summarizes the fold changes in gene expression, as determined by microarray analysis, for each treatment condition. Immunization with A91 or Cop-1 generally resulted in a downregulation of genes associated with inflammatory processes. Notably, statistically significant differences were observed exclusively in the A91-treated group when compared to both the PBS and Cop-1 groups. For clarity, gene expression fold changes in Table 1 are represented using a color-coded scheme: red indicates genes with a ≥1-fold increase, yellow represents genes with a ≥0.3-fold increase, and green denotes genes with a fold change <0.3. Among the A91-treated group, *Bmp2*, *Casp1*, *Casp3*, *Ccl2*, *Cebpb*, and *Cish* exhibited the most pronounced downregulation (average fold change < 0.3), suggesting potential suppression of pro-inflammatory and apoptotic pathways (Table 1).

Table 1. Fold change in gene expression from the microarray analysis across treatment groups

	Groups mean +/- SD			
Gen	PBS	A91	Cop-1	P value
Bmp2	1.76 +/- 0.11	0.28 +/- 0.23	1.04 +/- 0.47	0.001
Bmp3	1.34 +/- 0.38	1.74 +/- 0.45	1.1 +/- 0.28	ns
Casp1	1.38 +/- 0.38	0.26 +/- 0.17	1.04 +/- 0.47	0.001
Casp3	1.45 +/- 0.43	0.29 +/- 0.19	1.15 +/- 0.48	0.05
Ccl2	1.8 +/- 0.04	0.3 +/- 0.17	1.3 +/- 0.14	0.001
Ccl22	1.66 +/- 1.33	1.82 +/- 1.83	1.36 +/- 1.21	ns
Ccl3	1.31 +/- 0.30	0.63 +/- 0.64	0.89 +/- 0.41	ns
Cebpb	1.76 +/- 0.16	0.24 +/- 0.16	1.03 +/- 0.47	0.05
Cish	1.59 +/- 0.11	0.27 +/- 0.14	0.97 +/- 0.38	0.001
Socs2	1.61 +/- 0.29	0.85 +/- 0.24	0.81 +/- 0.13*	0.05
Socs3	1.31 +/- 0.40	0.49 +/- 0.40	0.96 +/- 0.45	0.05
Cx3cl1	1.22 +/- 0.32	0.55 +/- 0.53	0.9 +/- 0.44	ns
Cxcl10	1.32 +/- 0.30	0.51 +/- 0.50	0.94 +/- 0.44	ns
Cxcl2	1.33 +/- 0.29	0.5 +/- 0.48	0.97 +/- 0.43	ns
Il3ra	1.27 +/- 0.26	0.54 +/- 0.45	0.92 +/- 0.41	ns
Fgf1	1.54 +/- 0.49	0.68 +/- 0.48	0.91 +/- 0.34	ns
Fgf10	2.02 +/- 1.50	0.54 +/- 0.11	0.74 +/- 0.12	ns
Fgf11	1.2 +/- 0.41	0.48 +/- 0.30	0.88 +/- 0.39	ns
Fgf12	0.93 +/- 0.26	0.45 +/- 0.11	0.58 +/- 0.10	ns
Fgf13	1.22 +/- 0.40	0.49 +/- 0.45	0.91 +/- 0.51	ns
Fgf14	1.25 +/- 0.29	0.47 +/- 0.42	0.91 +/- 0.44	ns
Fgf15	1.21 +/- 0.30	0.44 +/- 0.37	0.91 +/- 0.42	ns
Fgf16	1.22 +/- 0.24	0.44 +/- 0.38	0.89 +/- 0.41	ns
Fgf17	1.21 +/- 0.34	0.44 +/- 0.35	0.92 +/- 0.46	ns
Fgf18	1.19 +/- 0.36	0.41 +/-0.31	0.87 +/- 0.46	ns
Fgf2	1.11 +/- 0.44	0.38 +/-0.27	0.85 +/ -0.46	ns
Fgf20	0.83 +/- 0.12	0.42 +/-0.20	0.63 +/- 0.04	ns
Fgf21	1.19 +/- 0.39	0.5 +/-0.45	0.9 +/- 0.50	ns

	Groups mean +/- SD			
Gen	PBS	A91	Cop-1	P value
Fgf22	1.18 +/- 0.30	0.46 +/-0.40	0.87 +/- 0.43	ns
Fgf23	1.22 +/- 0.35	0.44 +/-0.38	0.89 +/- 0.47	ns
Fgf3	1.19 +/- 0.37	0.45 +/-0.39	0.89 +/- 0.48	ns
Fgf5	1.11 +/- 0.44	0.45 +/-0.37	0.88 +/ -0.47	ns
Fgf6	1.11 +/- 0.43	0.39 +/-0.30	0.83 +/- 0.48	ns
Fgf7	1.11 +/- 0.45	0.41 +/-0.29	0.83 +/- 0.49	ns
Fgf8	1.19 +/- 0.40	0.45 +/-0.38	0.88 +/- 0.48	ns
Fgf9	1.18 +/- 0.47	0.52 +/-0.39	0.9 +/- 0.47	ns
Fgfbp1	1 +/- 0.23	0.57 +/-0.32	0.74 +/- 0.12	ns
Fgfr1	1.27 +/- 0.17	1.05 +/-0.46	0.94 +/- 0.28	ns
Fgfr2	1.17 +/- 0.33	0.5 +/-0.43	0.85 +/-0.40	ns
Fgfr3	1.17 +/- 0.30	0.48 +/-0.42	0.87 +/-0.40	ns
Frag1	1.16 +/- 0.32	0.45 +/-0.39	0.96 +/-0.41	ns
Ifrd1	1.17 +/- 0.38	0.42 +/-0.35	0.87 +/-0.47	ns
Il18bp	1.26 +/- 0.36	0.49 +/-0.46	0.92 +/-0.48	ns
Il10	1.2 +/- 0.71	0.63 +/-0.37	0.9 +/-0.19	ns
Il10ra	1.21 +/- 0.40	0.51 +/-0.32	0.85 +/-0.35	ns
Il11	1.21 +/- 0.34	0.48 +/-0.39	0.89 +/-0.46	ns
Il12a	1.18 +/- 0.35	0.47 +/-0.39	0.9 +/-0.46	ns
Il12b	1.14 +/- 0.35	0.5 +/-0.44	0.87 +/-0.41	ns
Il13	1.17 +/- 0.37	0.46 +/-0.39	0.88 +/-0.44	ns
Il15	1.2 +/- 0.21	0.61 +/-0.35	0.85 +/-0.27	ns
Il18	1.22 +/- 0.41	0.49 +/-0.44	0.86 +/-0.38	ns
Il1a	1.23 +/- 0.40	0.56 +/-0.49	0.97 +/-0.48	ns
Il1b	1.26 +/- 0.36	0.5 +/-0.41	0.93 +/-0.45	ns
Il1r1	1.23 +/- 0.37	0.51 +/-0.43	0.95 +/-0.47	ns
Il1r2	1.17 +/- 0.33	0.6 +/-0.55	0.92 +/-0.43	ns
Il1rap	1.71 +/- 0.52	0.5 +/-0.08	1.56 +/-0.13	0.05
Il1rl2	1.24 +/- 0.20	0.49 +/-0.22	0.85 +/-0.21	ns
Il1rn	2.03 +/- 2.12	0.65 +/-0.40	0.95 +/-0.58	ns
Il2	1.23 +/- 0.41	0.52 +/-0.42	0.87 +/-0.40	ns
Il24	1.42 +/- 0.62	0.58 +/-0.46	0.98 +/-0.44	ns
Il2ra	1.31 +/- 0.37	0.53 +/-0.44	0.99 +/-0.47	ns
Il2rb	1.26 +/- 0.33	0.52 +/-0.46	0.97 +/-0.43	ns
Il3	1.92 +/- 0.91	1.74 +/-0.91	1.78 +/-0.68	ns
Il4ra	1.17 +/- 0.38	0.46 +/-0.37	0.92 +/-0.46	ns
Il5	1.2 +/- 0.38	0.55 +/-0.47	0.93 +/-0.46	ns
Il5ra	1.2 +/- 0.38	0.5 +/-0.42	0.92 +/-0.47	ns

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	Groups mean +/- SD			
Gen	PBS	A91	Cop-1	P value
Il6	1.19 +/- 0.28	0.52 +/-0.48	0.97 +/-0.41	ns
Il6ra	1.31 +/- 0.34	0.55 +/-0.46	0.98 +/-0.42	ns
Il6st	1.24 +/- 0.33	0.52 +/-0.41	0.94 +/-0.42	ns
Il7	1.27 +/- 0.38	0.51 +/-0.37	0.99 +/-0.45	ns
Il8rb	1.24 +/- 0.39	0.49 +/-0.39	0.96 +/-0.48	ns
Il9r	1.23 +/- 0.41	0.47 +/-0.37	0.95 +/-0.49	ns
Ilf3	1.26 +/- 0.36	0.51 +/-0.46	0.95 +/-0.47	ns
Lta	1.16 +/- 0.39	0.46 +/-0.36	0.88 +/-0.48	ns
Ccl11	1.21 +/- 0.35	0.52 +/-0.43	0.9 +/-0.42	ns
Ccl17	1.2 +/- 0.24	0.57 +/-0.43	0.89 +/-0.29	ns
Ccl20	1.38 +/- 0.85	1.3 +/-0.56	1.41 +/-0.94	ns
Ccl4	1.22 +/- 0.32	0.53 +/-0.43	0.97 +/-0.42	ns
Tgfa	1.29 +/- 0.37	0.47 +/-0.34	0.97 +/-0.45	ns
Tgfb1	0.94 +/- 0.17	0.42 +/-0.15	0.74 +/-0.09	ns
Tgfb1i1	1.34 +/- 0.45	0.51 +/-0.40	1 +/-0.44	ns
Tgfb1i4	1.49 +/- 0.82	0.48 +/-0.34	0.66 +/-0.21	ns
Tgfb2	1.21 +/- 0.38	0.43 +/-0.33	0.9 +/-0.48	ns
Tgfb3	1.32 +/- 0.37	0.32 +/-0.26	1.32 +/-0.05	0.05
Tgfbr2	1.2 +/- 0.28	0.62 +/-0.45	0.96 +/-0.35	ns
Tgfbr3	1.28 +/- 0.35	0.52 +/-0.40	1.02 +/-0.43	ns
Klf10	1.31 +/- 0.39	0.49 +/-0.39	1.03 +/-0.45	ns
Tnf	1.21 +/- 0.30	0.57 +/-0.27	1.02 +/-0.37	ns
Tnfsf11	1.33 +/- 0.41	0.49 +/-0.41	1.01 +/-0.46	0.05
Tnfsf4	1.26 +/- 0.37	0.49 +/-0.37	0.97 +/-0.46	ns
Faslg	1.02 +/- 0.24	0.48 +/-0.21	0.85 +/-0.26	ns

The values represent relative expression levels compared to the Sham group. Statistical analysis was performed using the Kruskal–Wallis test, followed by post hoc Mann–Whitney U tests ($p < 0.05$). SD: standard deviation.

Among all the genes analyzed, only eleven exhibited statistically significant downregulation in the A91-treated group compared to the PBS and Cop-1 groups. Although the Cop-1 group showed a reduction in the expression of these genes, the differences were not statistically significant when compared to the PBS group (Table 2).

Table 2. Changes in gene expression of the different groups

	Groups mean +/- SD			
Gen	**PBS**	**A91**	**Cop-1**	**p compared with all the groups**
Bmp2	1.76 +/- 0.11	0.28 +/- 0.23	1.04 +/- 0.47	0.001
Casp1	1.38 +/- 0.38	0.26 +/- 0.17	1.04 +/- 0.47	0.001
Casp3	1.45 +/- 0.43	0.29 +/- 0.19	1.15 +/- 0.48	0.05
Ccl2	1.8 +/- 0.04	0.3 +/- 0.17	1.3 +/- 0.14	0.001
Cebpb	1.76 +/- 0.16	0.24 +/- 0.16	1.03 +/- 0.47	0.05
Cish	1.59 +/- 0.11	0.27 +/- 0.14	0.97 +/- 0.38	0.001
Socs2	1.61 +/- 0.29	0.85 +/- 0.24	0.81 +/- 0.13	0.05
Socs3	1.31 +/- 0.40	0.49 +/- 0.40	0.96 +/- 0.45	0.05
Il1rap	1.71 +/- 0.52	0.5 +/-0.08	1.56 +/-0.13	0.05
Tgfb3	1.32 +/- 0.37	0.32 +/-0.26	1.32 +/-0.05	0.05
Tnfsf11	1.33 +/- 0.41	0.49 +/-0.41	1.01 +/-0.46	0.05

The values represent relative expression levels compared to the Sham group. Statistical analysis was performed using the Kruskal–Wallis test, followed by post hoc Mann–Whitney U tests ($p < 0.05$). SD: standard deviation.

DISCUSSION

The present study provides insight into the complex and severity-dependent gene expression changes induced by immunization with neural-derived peptides (A91 and Cop-1) following severe spinal cord injury (SCI). Previous work by our laboratory demonstrated the neuroprotective and anti-inflammatory effects of these peptides in moderate SCI models;[7,8,19] however, these effects were significantly diminished under conditions of severe injury. Using a targeted microarray approach focused on inflammatory genes, the study reveals that only immunization with A91 significantly modulates the expression of a subset of inflammation-related genes, with limited efficacy observed for Cop-1.

The *Bmp2 gene* encodes a bone morphogenetic protein (BMP) involved in neural repair and astrocytic reactivity,[20,21] *Bmp2* was significantly downregulated in the A91 group. This contrasts with the sustained expression in PBS and Cop-1 groups and may suggest that A91 helps attenuate astrocyte-driven gliosis, a major impediment to axonal regeneration in SCI. [20,22] Interestingly, while *Bmp3 gene*, a known antagonist of canonical BMP signaling,[23] was overexpressed in all groups, its functional role in SCI remains undefined. This divergence highlights the nuanced regulation of the BMP pathway, where the balance between members (e.g., *Bmp2* vs. *Bmp3*) may influence lesion architecture and the potential for regeneration.[20,21]

One of the most striking findings was the significant downregulation of *Ccl2*, *Casp1*, and *Casp3* genes exclusively in the A91 group. *Ccl2 gene encodes for Ccl2 protein that* is a chemokine critical for monocyte and T-cell recruitment.[24] Its reduction could limit excessive immune infiltration and consequent secondary tissue damage. Fang et al.[25] reported that *Ccl2* modulates the PI3K/Akt pathway, impacting apoptosis through regulation of *Bax* and *Caspase-3.* Thus, the concurrent downregulation of *Caspase-3* (apoptosis marker) and *Caspase- 1* (pyroptosis mediator) further supports the hypothesis that A91 immunization shifts the post-injury environment toward neuroprotection by dampening cell death mechanisms.[25,26] Pyroptosis, a highly inflammatory form of programmed cell death mediated via the NLRP3 inflammasome and Caspase-1,[26,27] is known to exacerbate SCI. A91-suppression of *Casp1 gene*, along with *Cebpb gene* and *Il1rap gene*—both involved in inflammasome signaling—suggests it may partially inhibit inflammasome activation, reducing pyroptosis and preserving neural tissue.[28]

Furthermore, the study found significant suppression of *SOCS genes* (Suppressor of Cytokine Signaling) family —*Cish*,

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Socs2, and *Socs3*— only in the A91 group. While SOCS proteins typically act as negative feedback regulators of cytokine signaling,[29,30] *Socs3* has been implicated in excitotoxic neuronal death and inflammation-induced injury in the CNS.[31,32] Its reduction may reflect a compensatory mechanism or could result in enhanced activation of anti-inflammatory signaling via STAT3, which has shown neuroprotective roles.[31] Similarly, the reduction in *Tgfb3 gene*, that encode a TGF-β superfamily member regulating Th17/Th1 balance, may indicate suppressed neuroinflammatory polarization.[33] The reduction in *Tnfsf11 gene* (RANK), which influences dendritic cell survival and immune activation via non-canonical NF-κB pathways,[34] suggests broader immunomodulatory effects mediated by A91.

Importantly, although A91 significantly decreased the expression of several key genes involved in immune modulation, apoptosis, and chemotaxis, these molecular effects did not translate into evident neuroprotection or improved outcomes in the context of severe SCI, as shown in prior work by our group.[7,19] This discrepancy may be attributed to the highly deleterious microenvironment generated after severe injury, particularly in the more advanced stages of the lesion. Such a hostile environment, characterized by sustained oxidative stress, pro-inflammatory cytokine release, and cellular necrosis, could override the potential benefits of A91-induced gene modulation. Therefore, despite its promising immunomodulatory profile, A91's clinical efficacy appears limited under severe injury conditions. This disconnection between gene expression changes and functional outcomes highlights a critical area for future research. Investigating the temporal evolution of the post-injury microenvironment and its impact on therapeutic responsiveness will be essential to optimize the timing and context of peptide-based interventions.

Interestingly, while *Il1b*, *Il18*, and *Tnf genes* showed numerical decreases in the A91 and Cop-1 groups, the changes were not statistically significant. These cytokines are central to SCI pathology, and their persistent expression might explain the limited functional recovery observed in prior severe SCI studies using these peptides.[7,19] The lack of suppression in other chemokines genes, such as *Ccl20* and *Ccl22*, across all groups suggests that certain inflammatory circuits remain unresponsive to peptide immunization, possibly due to overwhelming injury-related damage-associated molecular patterns (DAMPs) that continuously activate NF-κB and MAPK pathways.[35,36]

Despite the similarities between A91 and Cop-1 in immune modulation goals.[3,12,15] their divergent gene regulation patterns observed here reinforce that even subtle biochemical differences can drastically alter immunological outcomes. For instance, Cop-1 failed to significantly downregulate any of the eleven key inflammatory genes modulated by A91, consistent with previous findings that A91 is more effective in moderate SCI, but less so in severe models.[7,19]

These results suggest that the neuroprotective potential of peptide immunization is not solely dependent on peptide structure, but also on the severity of the injury and the existing inflammatory milieu. In cases of severe SCI, where immune activation and tissue damage are more profound, the ability of immunomodulatory therapies to tip the balance toward repair is diminished. Therefore, optimizing the timing, dosage, and possibly combining A91 with other anti-inflammatory or neuroregenerative agents may be necessary to overcome this limitation.

CONCLUSION

The present study provides compelling evidence that A91, in comparison with Cop-1, induces a focused anti-inflammatory gene expression profile in severe SCI, particularly affecting genes associated with apoptosis (Caspase-3), pyroptosis (Caspase-1, Cebpb), chemotaxis (Ccl2), and key signaling regulators (SOCS3, Tgfb3). However, the beneficial effects of A91 on gene expression are not reflected in functional outcomes after severe SCI, likely due to the noxious microenvironment generated in later stages of injury. It is imperative that future studies prioritize the investigation of the way this environment interferes with therapeutic interventions. Further research is required to evaluate the following:

- Dose-dependent responses.
- Time-course gene expression dynamics.
- The correlation between molecular changes and histological and behavioral outcomes Elucidation of these relationships may facilitate refinement and optimization of therapeutic immunization strategies in the context of SCI.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Original research

Epidemiological Overview of Cervical Cancer and Human Papillomavirus Vaccination in the Yucatán Peninsula, Mexico (2014-2024): Challenges and Perspectives

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ABSTRACT

Introduction: Since 2006, cervical cancer (CC) has remained a significant public health issue in Mexico, ranking as the second leading cause of cancer-related mortality among women over the age of 25. However, epidemiological data on this disease remain scarce in the Yucatán Peninsula. This study reviews the prevalence and mortality of cervical cancer in the Yucatán Peninsula over the past ten years, as well as recent progress in human papillomavirus (HPV) vaccination coverage among girls aged 10 to 14. **Objective:** The aim is to provide relevant data to support decision-making in the primary prevention of cervical cancer. **Materials and Methods:** Official data were retrieved from the Ministry of Health and statistical reports from the National Institute of Statistics and Geography. Additionally, a systematic literature review was conducted from 2014 to 2024 using PubMed and Google Scholar databases, with Medical Subject Headings (MeSH) terms. **Results:** The results indicate that the states of Campeche, Yucatán, and Quintana Roo have among the highest national rates of HPV prevalence and cervical cancer mortality. Despite recent improvements in vaccination coverage since 2022, further efforts are needed to achieve the target of at least 70% coverage, in alignment with the 2030 global goals. **Conclusion:** Reaching this threshold is crucial to reducing future cervical cancer incidence and mortality in the region.

Key words: HPV; vaccination; CC; incidence; mortality.

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RESUMEN

Introducción: Desde el año 2006, el cáncer cervicouterino (CaCU) en México representa un problema de salud pública, ocupando el segundo lugar en mortalidad por cáncer en mujeres mayores de 25 años. La información generada en torno a la epidemiología de esta patología es escasa en nuestra región. Por ello, se revisaron la prevalencia y mortalidad de CaCU en la Península de Yucatán durante los últimos 10 años, además de analizar los avances en la cobertura vacunación contra el Virus del Papiloma Humano (VPH) en niñas de 10 a 14 años. **Objetivo:** El objetivo es aportar información importante que podría ser de utilidad para la prevención primaria del CaCU. **Materiales y Métodos:** Se realizó una búsqueda de información en fuentes oficiales de la Secretaría de Salud, reportes estadísticos del Instituto Nacional de Estadística y Geografía. Adicionalmente se llevó a cabo una búsqueda sistemática de literatura entre 2014 y 2024 en bases de datos como PubMed y Google Scholar, utilizando términos MeSH. **Resultados:** Los resultados muestran que los estados de Campeche, Yucatán y Quintana Roo tienen altas tasas de prevalencia de VPH y mortalidad por CaCU a nivel nacional. A pesar de los avances en la cobertura de vacunación desde 2022, aún se requiere alcanzar al menos un 70% de cobertura, según los objetivos 2030. **Conclusión:** Esto es crucial para disminuir la prevalencia y mortalidad en las próximas generaciones de mujeres en la región.

Palabras clave: VPH; vacunación; CaCU; incidencia; mortalidad.

INTRODUCTION

Cervical cancer (CC) is characterized by the uncontrolled growth, development, and multiplication of squamous cells in the transformation zone of the cervix. According to the World Health Organization (WHO), cervical cancer ranked eighth in incidence, with 661,021 new cases, and ninth in mortality, with 348,189 deaths reported in 2022.[1–3]

In Latin America, the association between human papillomavirus (HPV) infection and CC constitutes a major public health challenge, not only due to the high incidence reported in 2022 (ranging from 11.3 to 38.7 cases per 100,000 inhabitants) and mortality rates (5.2 to 18.3 deaths per 100,000 inhabitants),2 but also because of persistent structural barriers in prevention, diagnosis, and treatment programs. A recent analysis by Hernández-Silva et al. (2024) estimated the overall prevalence of HPV in Latin American women at 10.16%, with 8.52% corresponding to high-risk strains. Additionally, 1.83% of women were found to be co-infected with multiple genotypes simultaneously.[4]

Epidemiology of cc in Mexico: incidence, prevalence, and demographic distribution

According to the Global Cancer Observatory (GLOBOCAN 2022), **CC** has been the second leading cause of cancer-related mortality among women in Mexico, with a total of 10,348 new cases (9.3%) and 4,909 deaths (5.1%) reported in 2022. The estimated annual prevalence for 2022 was 13,960 cases, with an incidence rate of 23.3 new cases per 100,000 women.[5]

A descriptive cross-sectional study was conducted using data from the Institutional Cancer Registry of the Mexican Social Security Institute (IMSS) for the period 2018-2022. The study revealed that the majority of premalignant and malignant cervical lesions manifested in women between the ages of 35 and 54.[6] Furthermore, the 2024 report of the World Health Organization, entitled Situation Analysis of Cervical Cancer in the Americas, indicated that Mexico had an incidence rate of 13.2 per 100,000 and a mortality rate of 6.2 per 100,000 in 2022, ranking fourth lowest in Central America.[7]

Hpv vaccination coverage and strategies in Mexico: progress and 2030 goals

the WHO developed a plan titled Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem in response to global morbidity and mortality associated with CC. The primary objective of this strategy is to eliminate CC as a public health issue by promoting prevention, early detection, and effective treatment. The objective of the program is to reduce incidence rates to below 4 cases per 100,000 women, thereby preventing an estimated 300,000 CC deaths worldwide.

To achieve the targets set for the year 2030, the WHO introduced the “90-70-90” strategy, which outlines clear and measurable goals:

1. Vaccination: Ensure that 90% of girls worldwide are fully vaccinated against HPV before the age of 15.
2. Screening: Guarantee that at least 70% of women undergo high-precision screening, such as HPV DNA testing or cytology,by the age of 35, with a second screening by age 45.
3. Treatment: Ensure that 90% of women diagnosed with precancerous lesions or CC receive timely and appropriate treatment.[1]

Cervical cancer survival in Mexico

CC remains a major public health concern in Mexico, where survival rates continue to reflect deeply rooted structural inequalities in access to healthcare services.[8] A recent study based on data from the Catastrophic Health Expenditures Fund (FPGC) of the now-defunct Seguro Popular revealed that women diagnosed at early stages had a survival rate of 88.0%, whereas those diagnosed at metastatic stages had a survival rate of only 43.6%.[8] Moreover, the risk of death from CC increased by 0.3% with each additional year of age (HR = 1.003; 95% CI: 1.001-1.004), suggesting cumulative vulnerability among older women, particularly those facing barriers to accessing specialized care.[8]

This study aims to synthesize epidemiological and bibliographic evidence on the incidence of premalignant cervical lesions, HPV detection rates, and CC mortality across the Yucatán Peninsula, including the states of Campeche, Quintana Roo, and Yucatán, and to assess HPV vaccination coverage among girls and women.

METHODOLOGY

This study aimed to answer the research question: *What is the prevalence, incidence, and mortality rates of CC, and what is the HPV vaccination coverage in the Yucatán Peninsula between 2014 and 2024?*

A cross-sectional, observational, and descriptive study was conducted. The study focused on regional differences in comparison to the national average. The graphical representations were generated using data from epidemiological bulletins published by the National Institute of Statistics and Geography (INEGI). A linear smoothing model was employed to identify temporal trends from 2014 to 2024. This analysis was carried out in collaboration with Amphora Health, Mexico, using its Beluga Science platform, a digital tool designed for the management of scientific and epidemiological data, advanced statistical analysis, and data visualization.[9]

To obtain data on HPV vaccination coverage, reports from the National Institute of Public Health (INSP) and bulletins from the Ministry of Health (SSA) were used. The years for which data was obtained were 2015, 2020, and 2022–2023.

All statistical analyses were performed using Python (v3.11) to evaluate differences in HPV vaccination coverage between the Yucatán Peninsula and the national average. Mean values, standard deviations, confidence intervals, and p-values were calculated using Student's t-test, with statistical significance set at $p < 0.05$.

A systematic literature search was conducted in the PubMed and Google Scholar databases. In PubMed, MeSH terms included: ('Uterine Cervical Neoplasms'[Mesh] OR 'Cervical Cancer') AND ('Papillomavirus Infections'[Mesh] OR 'HPV') AND ('Incidence'[Mesh] OR 'Epidemiology') AND ('Mexico'[Mesh] OR 'Yucatán' OR 'Campeche' OR 'Quintana Roo') AND ('Vaccination'[Mesh] OR 'HPV vaccine'). Filters were applied for language (Spanish and English), publication date (2014-2024), and study type (original articles, systematic reviews, technical reports). In Google Scholar, search terms included both Spanish and English phrases such as "HPV vaccination Mexico Yucatán Campeche Quintana Roo," "cervical cancer incidence Mexico peninsula," and "cervical dysplasia and HPV Mexico."

Peer-reviewed publications retrieved from PubMed and Google Scholar were used to construct the contextual and conceptual framework of the study.

The selection of studies on HPV vaccination coverage and CC mortality followed specific inclusion criteria: only those reporting data disaggregated by state within the Yucatán Peninsula, or national data clearly applicable to the region, were considered. Priority was given to reports from the INSP platform and SSA bulletins, as these sources provide detailed, state, and municipality-level figures suitable for comparative statistical analysis.

Data extraction and quality assessment

The full process of article identification, selection, and exclusion for this systematic review is detailed in Figure 1, in accordance with PRISMA guidelines.

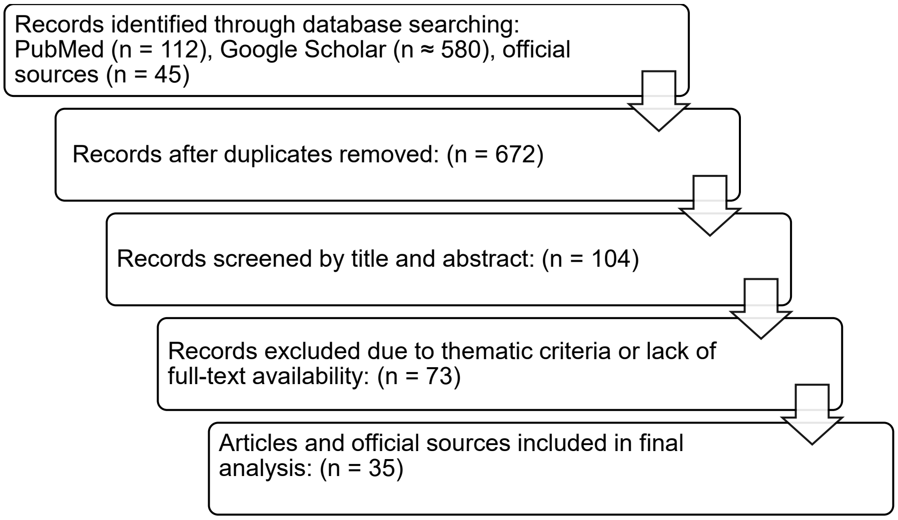

Figure 1. Stages of literature search and article process.

RESULTS

Incidence and Mortality of CC in Mexico

In 2017, a total of 306,675 deaths among women were recorded in Mexico, of which 42,891 (13.9%) were attributed to malignant tumors.[10,11] Among these, breast cancer and CC together accounted for approximately one-quarter (25%) of all cancer-related deaths in women.[11] The National Institute of Statistics and Geography (INEGI), in its 2018 report titled *"Statistics on the Occasion of World Cancer Day"*, analyzed data from the 2011-2016 period. This analysis showed that the highest incidence of CC occurred among women aged 30 to 59 years.[12]

In 2020, CC was the second most frequently diagnosed cancer and the second leading cause of cancer-related mortality among Mexican women, with an estimated 9,439 new cases and 4,335 deaths. This corresponded to an incidence rate of 12.6 and a mortality rate of 5.7 per 100,000 women.[13]

In 2021, the Mexican Social Security Institute (IMSS) reported 1,155 new cases and 1,059 deaths from CC among its insured population, corresponding to incidence and mortality rates of 2.26 and 5.23 per 100,000 women, respectively.[14] That same year, national health authorities reported an overall increase in CC burden, with 3,058 newly diagnosed cases and 4,111 deaths attributed to the disease.[10]

Incidence and prevalence of cc and hpv in the Yucatán Peninsula

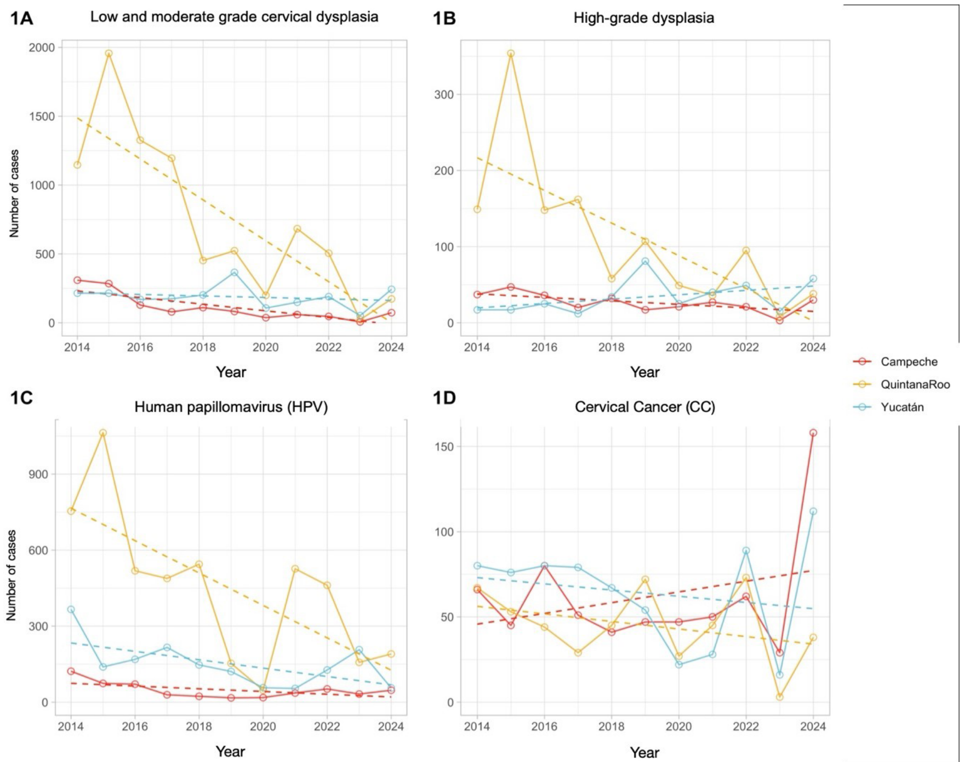

Figure I. Incidence of cervical dysplasia and cervical cancer in the Yucatán Peninsula, Mexico (2014–2024). (1A) shows the annual number of cases of mild to moderate cervical dysplasia among women in the three states. (1B) presents the annual number of cases of severe dysplasia and carcinoma in situ. (1C) depicts the annual number of HPV cases. (1D) illustrates the annual number of cervical cancer cases among women in the three states. Source: Prepared by the authors in collaboration with Amphora Health, Mexico, using the Beluga Science platform and based on epidemiological bulletins from the Ministry of Health (SSA). The graphs display state-specific data using the following color scheme: Quintana Roo (yellow), Campeche (red), and Yucatán (blue).

This study analyzed the annual number of cases among women (Figure 1), focusing on cumulative totals of low- and moderate-grade cervical dysplasia (Figure 1A), high-grade dysplasia (Figure 1B), annual HPV infection cases (Figure 1C), and CC (Figure 1D) recorded between 2014 and 2024 in the states of Campeche, Quintana Roo, and Yucatán. Figures 1A and 1B show that the state of Quintana Roo consistently exhibited the highest incidence rates of cervical lesions, both low- to moderate-grade and high-grade dysplasia, across the Yucatán Peninsula. Notably, between 2015 and 2017, an annual average of 1,416 cases of low, to moderate grade dysplasia and approximately 203 cases of high-grade dysplasia were recorded. From 2019 onward, both types of cervical lesions showed a steady decline, with particularly notable reductions observed between 2023 and 2024.

Figure 1D indicates that CC cases peaked between 2019 and 2022, with an average of 171 cases per year. In contrast, Campeche consistently reported fewer cases than Quintana Roo and Yucatán, although it experienced distinct spikes in both low- and high-grade dysplasia from 2016 to 2018 (Figures 1A and 1B). Nevertheless, Campeche maintained a relatively stable average of approximately 54 CC cases annually throughout the 2014-2022 period.

In Yucatán, the number of cases peaked in 2019, with an annual average of 316 cases of low- to moderate-grade dysplasia and a concurrent increase in high-grade dysplasia, reaching 81 cases (Figures 1A and 1B). It is important to note that throughout the study period, Yucatán and Campeche consistently reported the lowest incidence rates

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of both mild and severe cervical dysplasia compared to Quintana Roo. However, as shown in Figure 1D, the trend for CC revealed a more variable distribution. During the early years of the study (2014–2019), no single state predominated in terms of case numbers. In 2024, the incidence of CC rose across all three states, with Campeche experiencing a particularly marked increase, rising from fewer than 30 annual diagnoses to 74.

Regarding HPV infection (Figure 1C), a sustained decline in detection rates was observed over the 2014-2024 period. Quintana Roo, which reported over 300 cases annually in 2014, experienced a gradual reduction to fewer than 100 cases by 2023.

CC Mortality in the Yucatán Peninsula

CC continues to disproportionately affect certain regions of Mexico, particularly the southeastern states. According to data published by the National Center for Gender Equity and Reproductive Health in August 2019 (5), the states with the highest CC mortality rates were Chiapas (19.7%), Quintana Roo (17.7%), Morelos (16.0%), Yucatán (15.6%), and Veracruz (14.4%). Notably, two of the five states with the highest mortality are in the Yucatán Peninsula, underscoring the region's priority status for public health interventions.

In 2023, INEGI reported 4,504 CC deaths nationwide, with the majority occurring among older women. Specifically, 33.9% of deaths were recorded in women aged 65 years and older, followed by 21.8% in those aged 45-54, and 21.2% in the 55–64 age group.[15] These age-related patterns highlight the need to strengthen screening and early detection programs for older women, who remain at increased risk for late-stage diagnosis.[15]

A study by Sánchez-Mercader et al. (2021) analyzed CC mortality in Yucatán between 2013 and 2017 using SSA data.16 The findings revealed that women over 70 years of age had mortality rates consistently higher than the national average. For Yucatán, mortality rates (per 100,000 women) were: 4.76 (2013), 5.03 (2014), 4.91 (2015), 5.07 (2016), and 5.17 (2017). In contrast, the national averages for these years ranged from 3.16 to 3.43, indicating a persistent regional disparity.[16]

An analysis of female mortality in Quintana Roo, based on the 2015 report by the National Institute for Women and cited by Guarneros-Cuellar et al. (2016), documented a CC mortality rate of 15.2 deaths per 100,000 women. This rate exceeded that of breast cancer in the same state and period, which was reported at 9.7 deaths per 100,000 women.[17]

However, despite a thorough search, no recent or official data on CC mortality in Campeche was found. This lack of localized data restricts the possibility of conducting a thorough epidemiological assessment of the Yucatán Peninsula, thereby emphasizing the necessity of enhancing cancer surveillance systems in the region.

HPV Vaccination Coverage in the Yucatán Peninsula, Mexico

Clinical trials have demonstrated that HPV vaccination significantly reduces infection rates and, consequently, the likelihood of developing precancerous lesions and CC in women.[18] As part of its global elimination strategy, the WHO has established a target of 90% vaccination coverage among girls by age 15 by the year 2030.[19]

Although national-level data on HPV vaccination coverage in Mexico remain limited, the *Vaccination Atlas* published by the National Institute of Public Health (INSP) provides regional data for girls aged 10-14 in the Yucatán Peninsula (Table I).[20]

Table I. HPV vaccination coverage in females aged 10-14 years in the Yucatán Peninsula, Mexico, based on recorded vaccine doses in 2015 and 2020 (percentage values)

Peninsula States	Year 2015	Year 2020
Quintana Roo	29%	10%
Yucatán	32%	20%
Campeche	30%	16%

Source: Elaborated by the authors based on an analysis of data from the study "National Institute of Public Health, Center for Research in Evaluation and Surveys, Atlas of Coverage of the HPV Vaccination Program".

In 2015, Quintana Roo reported an HPV vaccination coverage rate of 29%, with the highest municipal rate observed in Bacalar (46.2%) and the lowest in Playa del Carmen (11.6%). By 2020, this rate had dropped sharply to 10%, likely due to disruptions caused by the COVID-19 pandemic.[20] That same year, the state of Yucatán achieved a coverage rate of 32%. Within the state, the municipality of Ticul reported the highest coverage (54.9%), while Motul recorded the lowest (2.8%).[20] Notably, Yucatán, the most populous state in the region, lacked vaccination data for several of its 116 municipalities. In contrast, Campeche reported a statewide coverage of 30% in 2015 and, unlike the other two states, provided vaccination data for all of its municipalities.[20] The municipality of Tenabo recorded the highest rate at 42.8%, whereas the state capital, Campeche, had the lowest at 17.6%.[20]

To assess progress in HPV vaccination coverage, data from the National Institute of Public Health (INSP) for the years 2022-2023 show a notable increase across the region. In Campeche, coverage reached 65.6% in 2022 and rose to 74.8% in 2023. Similarly, Yucatán reported a coverage rate of 63.1% in 2022, increasing to 73.9% in 2023.[20] In contrast, the state of Quintana Roo reported a coverage rate of 56.5% in 2022, which declined to 53.2% in 2023, a 3.3% decrease, making it the only state in the Yucatán Peninsula to exhibit a reduction during this period. At the national level, coverage stood at 39.7% in 2022 and rose substantially to 74.4% in 2023, reflecting significant progress in vaccination efforts across the country (Table II).[20] It is important to clarify that the data for individual municipalities was sourced directly from the INSP platform, rather than being extracted from Tables I and II.

Table II . HPV Vaccination Coverage (Cumulative, 2022–2023) in Girls Aged 10–14 Years in the Yucatán Peninsula and Nationally, Mexico

	2022 (%)	2023 (%)
National Average	39.7	74.4
Quintana Roo	56.5	53.2
Campeche	65.6	74.8
Yucatán	63.1	73.9

Source: Prepared by the authors based on data from the National Institute of Public Health, Center for Research in Evaluation and Surveys. Atlas of Coverage of the HPV Vaccination Program.

Table II presents a comparative analysis of HPV vaccination coverage in girls aged 10-14 across the states of the Yucatán Peninsula and the national average for the years 2022 and 2023. The data highlight notable differences in both the scale and consistency of immunization efforts during this period. In 2022, Table III shows that the average HPV vaccination coverage across the Yucatán Peninsula reached 61.73%, significantly higher than the national average of 39.7%. This difference was statistically significant ($p = 0.0148$) and was accompanied by low inter-state variability, indicating a more consistent and effective implementation of vaccination strategies within the Peninsula.

In contrast, although national coverage increased sharply to 74.4% in 2023, surpassing the peninsular average (which ranged from 53.2% in Quintana Roo to 74.8% in Campeche), the difference between the national and regional averages was not statistically significant ($p = 0.397$). Therefore, no definitive conclusion can be drawn regarding a true difference in vaccination coverage between the two levels for that year.

Table III. Statistical Comparison of National HPV Vaccination Coverage vs. the Yucatán Peninsula Average (Campeche, Quintana Roo, Yucatán), Cumulative Period 2022–2023

Indicator	Period 2022	Period 2023
National coverage average	39.7%	74.4%
Average in the peninsula (Campeche, Quintana Roo, Yucatán)	61.73%	67.3%
Standard deviation	4.70%	12.38%
95% confidence interval	(50.05%, 73.41%)	(44.94%, 89.65%)
P-value	0.0148	0.397

Source: prepared by the authors based on data from the National Institute of Public Health, Center for Research in Evaluation and Surveys, Atlas of HPV Vaccination Program Coverage.

The statistical comparison presented in Table III demonstrates that, in 2022, the average HPV vaccination coverage in the Yucatán Peninsula (61.73%) was significantly higher than the national average (39.7%), with a p-value of 0.0148 and a narrow confidence interval, indicating both consistency and significance in the regional efforts. However, in 2023, despite continued improvements, the peninsular average (67.3%) was slightly lower than the national average (74.4%), and this difference was not statistically significant ($p = 0.397$), suggesting no meaningful variation between the two levels during that year. These trends make it clear that sustained and coordinated efforts are needed at federal, state and local levels to strengthen vaccine supply chains and reinforce immunization campaigns. These actions are essential to achieving the 90% coverage target by 2030 and to significantly reducing the incidence and mortality associated with CC.[19,21-23]

DISCUSSION

The epidemiological patterns of CC in the Yucatán Peninsula reveal significant disparities among its three states:

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Campeche, Yucatán, and Quintana Roo. These differences reflect a range of socioeconomic, structural, and health-care-related factors. For example, Sánchez-Mercader et al. (2021) emphasized the importance of considering health-care access, coverage of primary and secondary prevention strategies, social context, and the proportion of Indigenous populations when analyzing CC mortality in Yucatán.[16]

A key finding of this study is the paradox observed in Campeche and Yucatán: both states report low incidence of cervical dysplasia and HPV infection, yet they show an increasing number of CC cases. This trend suggests potential shortcomings in secondary prevention, particularly in screening programs. These shortcomings result in undetected lesions that progress to more advanced stages without timely diagnosis or treatment.[24-26] In contrast, Quintana Roo, initially characterized by high rates of HPV infection, cervical dysplasia, and CC incidence, has shown notable reductions across all three indicators. These improvements may be attributed to more effective implementation of screening programs, improved follow-up of positive cases, and broader HPV vaccination coverage.[26]

Ideally, early detection programs should lead to an increased diagnosis of low- or high-grade dysplasia and a corresponding decrease in invasive cancer incidence. However, national data indicate that over 50% of CC cases in Mexico are still diagnosed at advanced clinical stages, pointing to systemic failures in healthcare access and program effectiveness, particularly in socially and economically marginalized areas.[4,23] A study published in the Journal of Global Oncology by Unger-Saldaña et al. (2018) revealed that in public hospitals in Mexico City, only 9.5% of CC cases were diagnosed as carcinoma in situ, and just 16.9% were detected at Stage I. Alarmingly, over 60% were identified at stages II through IV, and only 15% were diagnosed through screening, most patients sought care due to the onset of symptoms.[27]

Similarly, Arango-Bravo et al. (2022), analyzing data from the national cohort of women treated under the Catastrophic Health Expenditures Fund, found that only 24.5% of CC cases were diagnosed at early stages (IA–IB1), while 68.5% were classified as locally advanced (IB2–IIIB), and 6.9% were already in advanced stages.[28] In this context, the trends observed in Yucatán are of particular concern. While the state reported relatively low rates of mild and moderate dysplasia, there was a sharp increase in cervical cancer (CC) incidence in 2019. This suggests possible weaknesses in screening systems, follow-up protocols or referral pathways.[16]

The situation is even more striking in Campeche, where, throughout the 2014-2024 period, the state consistently reported the lowest incidence of both dysplasia and HPV infection. Figure 1C shows a flat trend line, with fewer than 50 new HPV cases reported annually and minimal year-over-year variation. Rather than reflecting effective disease control, this pattern more likely points to limited diagnostic capacity and weak surveillance systems, possibly due to underutilized screening tools or narrow diagnostic criteria (e.g., HPV testing conducted only after detecting severe dysplasia or cancer).[29]

Unexpectedly, Campeche reported the highest number of new cervical cancer (CC) cases in 2024, with 220 cases, surpassing Yucatán (185) and Quintana Roo (173) (Figure 1D). This abrupt increase warrants further investigation into barriers such as access to healthcare, the availability of diagnostic infrastructure and sociocultural factors that may hinder the early detection and timely treatment of precancerous lesions.[24–26]

As highlighted by León-Maldonado et al. (2024), one of the main reasons for underreporting or the absence of HPV and dysplasia data in certain regions of Mexico is the limited coverage of CC screening programs and the restricted availability of high-sensitivity diagnostic technologies, such as HPV DNA testing. (29). These challenges are further exacerbated by entrenched sociocultural, geographic, and systemic barriers that continue to limit the reach and effectiveness of preventive services, particularly among women of reproductive age in rural and Indigenous communities.[29]

HPV vaccination remains the cornerstone of primary prevention. Although coverage in the Yucatán Peninsula improved notably between 2022 and 2023, rates still fall short of the 90% threshold recommended by the WHO to achieve herd immunity.[1,20] The 2023 decline observed in Quintana Roo, contrasting with improvements in Campeche and Yucatán, is particularly concerning. In some municipalities of Yucatán and Quintana Roo, vaccination coverage remains below 15%, underscoring the inequitable distribution of immunization efforts.[20] Evidence shows that HPV vaccination can reduce the incidence of high-grade cervical dysplasia by up to 87% when administered before sexual debut.[30] However, in Mexico, acceptance and implementation of HPV vaccination programs continue to be limited by sociocultural resistance, misinformation, and logistical challenges associated with school-based vaccination campaigns.[31] A comprehensive strategy should include a community-based health education initiatives targeting parents and caregivers.

Currently, Mexico primarily uses the bivalent vaccine (HPV types 16 and 18) and, to a lesser extent, the quadrivalent vaccine (types 6, 11, 16, and 18).[32,33] However, several high-risk genotypes that are prevalent in the Mexican population—such as types 31, 33, 45, and 52, are not covered by these formulations. This gap may limit the long-term impact of vaccination on CC incidence at the national level.[34]

Anaya Rodríguez et al. (2024) argue that transitioning to the nonavalent vaccine, which protects against nine genotypes, including the most prevalent in Mexico (6, 11, 16, 18, 31, 33, 45, 52, and 58), would significantly enhance the effectiveness of the national vaccination program.[33] However, implementing this transition would require political commitment, sustainable funding, coordination with international suppliers, and the revision of national operational guidelines. Therefore, the selection of vaccine type should be informed by scientific evidence and cost-effectiveness analyses tailored to the country's specific epidemiological profile.[33]

Additionally, Guzmán Tapia et al. (2024) emphasize the importance of including males in HPV vaccination programs. Males not only serve as asymptomatic carriers and transmitters of the virus but are also at risk for HPV-related diseases such as anogenital warts and malignancies of the anus, oropharynx, and genital tract.[34] In many high-income countries, the nonavalent vaccine is routinely administered to both sexes starting at age 9, with documented effectiveness exceeding 90% in preventing these conditions.[34] In Mexico, the inclusion of males in national HPV vaccination efforts is expected to begin officially in 2025. While this is a positive development, its impact on achieving herd immunity is likely to be delayed, with full benefits only observable in the long term.[33]

Parental acceptance of HPV vaccination remains a crucial determinant of uptake. Many caregivers lack awareness of the vaccine's role in cancer prevention or express concerns about its safety and efficacy.[32] This presents an opportunity for health authorities to collaborate with schools and community leaders to disseminate evidence-based information and facilitate informed parental consent, key to increasing adolescent vaccination rates in the country.[32]

From a bioethical perspective, Bayefsky (2021) argues that mandatory HPV vaccination can be ethically justified when voluntary strategies fail to achieve sufficient coverage.[35] According to the author, mandates, when implemented with transparent communication and culturally sensitive approaches to informed consent, can promote social justice, reduce health inequities, and protect vulnerable populations.[35] In the case of the Yucatán Peninsula, a multisectoral response is urgently needed. This includes improving screening registries, actively following up on suspected cases, and expanding access to high-sensitivity screening methods such as HPV DNA testing.

LIMITATIONS AND PERSPECTIVES

While this study provides a comprehensive overview of the epidemiological landscape of CC and HPV vaccination coverage in the Yucatán Peninsula, several limitations must be acknowledged. The availability and consistency of official data at the municipal level varied across the three states analyzed, limiting the precision of intra-regional comparisons and potentially affecting the accuracy of localized trend assessments. Special attention should be given to the availability and deployment of molecular HPV detection tools and the adequacy of medical supplies for effective diagnosis and clinical management. Such multidimensional approaches are essential for identifying systemic gaps and designing evidence-based, targeted interventions aimed at improving prevention, early detection, and care, particularly among vulnerable and underserved communities in the region.

CONCLUSION

The findings of this study reveal persistently high prevalence and incidence rates of CC and HPV infection, alongside insufficient HPV vaccination coverage across many municipalities in the Yucatán Peninsula. These patterns underscore significant inequities in the implementation of both primary and secondary prevention strategies throughout the region. Effectively addressing this public health challenge will require a multifaceted approach that extends beyond the administration of the HPV vaccine. Public health policies must be restructured to ensure equitable access to vaccination, screening, and treatment services, particularly in rural, Indigenous, and underserved communities. This research provides valuable insights that can inform health policy development and support the design of evidence-based strategies aimed at increasing HPV vaccination coverage, strengthening early detection programs, and ultimately reducing the CC burden in this high-risk region of Mexico.

CONFLICT OF INTEREST DECLARATION

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

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Review Article

Immunological insights into iatrogenic fungal meningitis caused by *Fusarium solani*

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ABSTRACT

Fungal meningitis has emerged as a significant public health problem, with outbreaks of the fungus *Fusarium solani* have been recorded in different locations exhibiting high pathogenicity and the serious central nervous system infections. Statistical studies demonstrate that the incidence of neuroinfections caused by *Fusarium solani* are in its majority presented in women (95%), with 88% having a history of obstetric-gynecological procedures, such as cesarean sections, or those involving intrathecal anesthesia. A literature review has been performed to elucidate the mechanisms implied in the immunological response to fungal neuroinfections caused by *Fusarium solani*. 18 articles found in different databases including PubMed, Cochrane Library and Scopus were incorporated in the present article. A critical knowledge gap regarding the evasion mechanisms employed by *Fusarium solani* to overcome the barriers of the nervous system. Further research in neuroimmunology is crucial in order to establish new therapeutic approaches to treat these infections.

Key Words: central nervous system; neuroinfection; fungus; meningitis; fusarium solani; anesthesia; iatrogenesis.

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RESUMEN

La meningitis fúngica ha surgido como un importante problema de salud pública, con brotes del hongo *Fusarium solani* registrados en diferentes regiones, exhibiendo alta patogenicidad y causando graves infecciones del sistema nervioso central. Estudios estadísticos demuestran que la incidencia de neuroinfecciones causadas por *Fusarium solani* se presenta mayoritariamente en mujeres (95%), con un 88% de casos relacionados con procedimientos obstétrico-ginecológicos, como cesáreas, o aquellos que involucran anestesia intratecal. Se realizó una revisión de la literatura para dilucidar los mecanismos implicados en la respuesta inmunológica a las neuroinfecciones fúngicas causadas por *Fusarium solani.* Se incorporaron 18 artículos encontrados en diferentes bases de datos, incluyendo PubMed, Cochrane Library y Scopus, en el presente artículo. Existe una importante brecha de conocimiento con respecto a los mecanismos de evasión empleados por *Fusarium solani* para superar las barreras del sistema nervioso. La investigación adicional en neuroinmunología es crucial para establecer nuevos enfoques terapéuticos para tratar estas infecciones.

Palabras clave: sistema nervioso central; neuroinfección; hongos, meningitis; fusarium solani; anestesia; iatrogenia.

INTRODUCTION

Meningitis is defined as inflammation and irritation of the meninges. In fungal meningitis, the meninges are infected and inflamed due to an increase in pressure secondary to the creation of an abscess, granuloma, cyst, etc. These intracranial masses increase pressure because of the subarachnoid space's obstruction, blocking cerebrospinal fluids drainage. This increase in pressure generates the symptoms that patients refer to such as severe headaches, nausea, vomiting, visual alterations, neurological deficits, or even convulsions.

Its diagnosis relies on classic clinical signs such as nuchal rigidity, Kernig's sign, and Brudzinski's sign. These signs work on the principle that by stretching the inflamed meningeal membranes, it will cause detectable irritation in the body. Positive signs increase the likelihood of a meningitis diagnosis, while their absence reduces this probability. They are most effective when combined with other historical and examination features to provide a comprehensive clinical assessment.[1]

Fungal meningitis, however, is particularly challenging to diagnose due to its nonspecific symptoms and often the absence of meningeal irritation signs. This difficulty in diagnosis results in delayed treatment, leading to higher rates of morbidity and mortality.[2] The complications from which meningitis derives have a great influence on mortality since they compromise brain tissue by generating chronic inflammation and subjects it to frequent hypoxic events. The most common and feared complication is the rupture of fungal aneurysms. A fungal aneurysm is highly mortal because of its rapid progress to hemorrhagic complications, that severely compromises patient´s lives. At the same time, one of the biggest concerns of medical personnel is that the elevation of intracranial pressure rises enough to herniate the tonsils of the cerebellum, compressing the cardiorespiratory center, resulting in respiratory failure, stupor, coma, arrhythmias, and even cardiac arrest.[3]

By May 2023, outbreaks of fungal meningitis had been recorded in states in the north of Mexico, such as the case of Durango, where 1,801 cases have been reported, it is of special interest that 95 % of the cases correspond to female patients, and 88 % of these cases with a history of gynecological-obstetric procedures, such as cesarean section, unfortunately there have been 39 deaths related to the outbreaks to that date. Since October 5, 2022, when the first cases were reported, and so far, it has been recorded that 31 of the cases have a positive PCR result for *Fusarium solani* fungus species.[4]

Between 1974 and 2022, 26 cases of neuroinfections caused by *Fusarium* were identified in the literature. In contrast to the recent outbreak, 60% of the individuals had underlying hematologic malignancy and 16% received immunosuppressive therapy. Given that many of the reported cases occurred before the widespread clinical use of voriconazole, most of the patients were managed with amphotericin B monotherapy.[5]

MATERIALS AND METHODS

A systematic review was carried out, based on the main globally recognized scientific databases, such as PubMed, Cochrane Library and Scopus. The terms ("Neuroinfection" AND "Fungus" OR "*Fusarium solani*"), ("Meningitis" AND

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"*Fusarium solani*"), ("Neuroinfection" AND "Anesthesia" AND "*Fusarium solani*") allowed to delimit the results with greater specificity oriented to iatrogenic meningitis by *Fusarium solani*. In addition, combinations of keywords were made that placed greater emphasis on the available treatments and on the therapeutic interventions applicable to this pathology. 18 articles from 2014 to 2024 were included in this review, focusing only on those with significant clinic and therapeutic relevance. Articles outside the temporal range, not indexed in the selected databases, or lacking a relevant focus on immunological and therapeutic approach were excluded.

RESULTS

Fungal neuroinfections

Although it is estimated that there are millions of species of fungi, only 70,000 have been identified, of which 300 have been classified as pathogenic for humans, and only 10-15 % can invade the central nervous system. Fungi need environments with organic matter and water to develop, resources that are found in hosts such as humans. How these organisms reach the body is usually due to direct contact with the skin, mucous membranes, or vascular system, the inhalation of their spores, or their direct inoculation. Generally, fungi do not tend to infect humans and in the case of an infection, the mechanisms of the immune system can prevent its dissemination; however, if these mechanisms fail to contain these agents, they can reach the meninges, cross the blood-brain barrier (BBB) and finally reach the central nervous system (CNS).

It is not common for this type of fungal infection to be transmitted from patient to patient, neither having a high incidence, however, various risk groups are more susceptible to fungal infections, such as individuals with HIV/AIDS, solid-organ transplants, hematological diseases, extensive burns or immunodeficiencies. However, in the reported outbreaks, the circumstances of the patients were different, as they were immunocompetent patients who have undergone surgical interventions of the nervous system, such as a lumbar puncture.[6-7]

Fusarium solani

Among the filamentous hyaline fungi is the genus *Fusarium*, which includes more than 200 different species, among which some agents are pathogens for humans, such as *F. solani, F oxysporum, F. verticillioides, and F. proliferatum, with F. solani* being the most resistant and lethal species of them. *Fusarium solani* can cause superficial infections such as onychomycosis and keratitis or disseminate throughout the system and generate serious pulmonary infections, meningitis, and brain or vertebral abscesses (Figure 1).

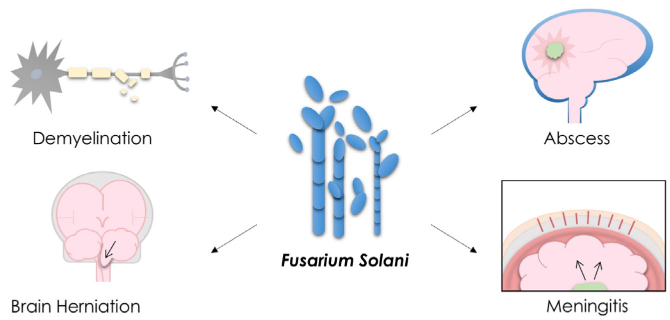

FIGURE 1. Impact of *Fusarium solani* at central nervous system level. The repercussions of fungal infections are mainly characterized by demyelination, abscesses, brain herniation and meningitis.

There are also different virulence factors in the *Fusarium* genus, such as mic toxins that suppress both cellular and antibody-mediated immune response, or other toxins such as Fumonisin B1, its mechanism of action in central nervous system infections consists of causing axons demyelination, in addition to damaging microglia by altering cellular respiration, and altered cellular respiration is a result of affecting the phospholipid membrane.[3,6] Another very relevant factor in fusariosis is their adaptability to environments with very few oxygen availability, by activating the processes of glycolysis and oxidative phosphorylation, which favor inflammation.[7]

The incidence of fusariosis varies geographically, with higher rates reported in tropical and agricultural regions. However, in recent years, outbreaks of meningitis and endophthalmitis caused by *Fusarium* have been documented in urban areas. These outbreaks have been linked to batches of contaminated parenteral drug formulations, as a result of poor aseptic manufacturing methods and the persistence of *Fusarium* within the production facilities, since this species is capable of persisting in drains and pipes, rubber sealants, cosmetics, among others.[8] Therefore, the administration of a contaminated drug can be related to an infection with this fungus, in this way, there is the hypothesis that the main entry route for *Fusarium solani* was during the epidural or spinal blockade before a cesarean section.

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Recent studies found that *Fusarium solani* exhibits a concerning tropism for the cerebral vasculature, leading to severe vasculitis and arterial dissection. This predilection may contribute to an increased risk of vertebrobasilar complex vasculitis (CVC) in patients affected by the current fungal meningitis outbreak. While the ascending spread of infection from the lumbar epidural space is a possible explanation, the full extent of *Fusarium´s* angioinvasive nature remains to be elucidated.[9]

Fusarium solani infections present a significant challenge due to the inherent resistance of these fungi to many antifungal classes; it is well-documented to have intrinsic resistance to echinocandins. The intrinsic resistance of *Fusarium* likely arose in the environment as a survival mechanism; it has developed efflux pumps that effectively combat plant-produced antimicrobials and tebuconazole. Furthermore, global warming might be contributing to increased virulence in some *Fusarium* species. For example, thermotolerance has been observed in the *Fusarium graminearum* complex, threating food security and leading to increased fungicide use in agriculture, which could further exacerbate antifungal resistance in the future.[5]

Role of the immune system

When a *Fusarium* infection occurs due to direct exposure of the tissue to the agent, before entering the central nervous system, it encounters a barrier generated by the meninges, where the fungus can lead to the formation of abscess or granulomas, causing a significant elevation of the intracranial pressure.

During systemic infections *Fusarium* may disseminate through the bloodstream to the CNS. The BBB restricts the fungal entry, limiting the infection to vasculature. However, because of immunosuppression, mechanisms of immunological evasion, or a high inoculum in immunocompetent patients, the fungus can disrupt this barrier and spread to CNS parenchyma, which may result in encephalitis or brain abscesses.[10] This underscores the importance of generating therapies that reinforce central nervous system barriers.

When *Fusarium* overcomes the primary barriers of the innate immune system such as phagocytosis, it is detected by the adaptive immune system through the recognition of its cell wall of chitin and β-glucan employing specific receptors and then the antigenic presentation is carried out by microglia and dendritic cells. However, the presence of immune cells in the CNS can cause irreparable damage due to the limited regeneration capacity of the resident cells. In addition, the recruited immune cells can contribute to the spread of fungi through the "Trojan horse" mechanism. The involvement of microglia and antigen-presenting cells may offer potential therapeutic targets related to immune activation and modulation.

Subsequently, both an inflammatory response is activated, as well as an anti-inflammatory response mediated by the type and number of cytokines produced by microglia and perivascular macrophages, the predominance between these types of response depends directly on the genetic susceptibility of the patient.[5,11] Also, T cells, astrocytes, and endothelial cells inhibit fungal growth by producing cytokines (IFN- γ, TNF-α, IL-1β, IL-6, and IL-12), chemokines, nitric oxide and superoxide anion, and by the expression of MHC I and II molecules.[12]

Neutrophils have a critical role in controlling inflammatory cellular reaction, as they provoke damage to hyphae of Fusarium by phagocytosis enhanced by G-CSF and IL-15, also enhanced by IL-8 and direct damage mediated by *Fusarium´s* hyphae. Patients with prolonged neutropenia, graft-versus-host disease and corticosteroid use exhibit increased risk for fusariosis. This observation highlights the relevance of neutrophil recruitment in combating these infections. Moreover, it suggests the potential applications of neutrophils to targeted drug delivery as shown in Figure 2.[13]

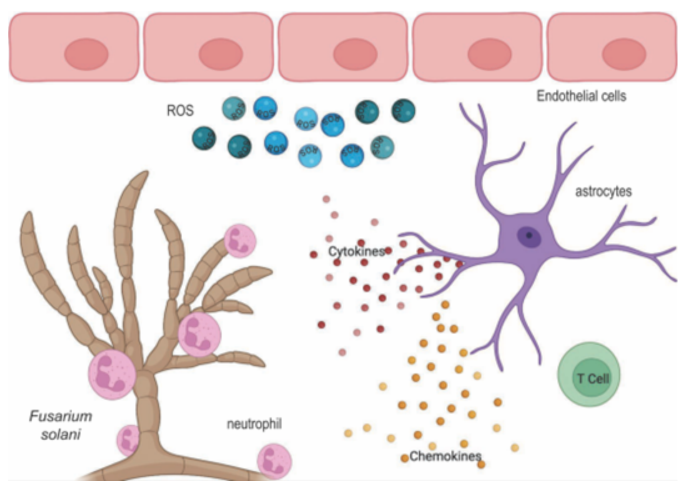

Figure 2. Inmune response to *Fusarium solani*. Multiple cells are involved in the response to *F. Solani* neuroinfection, such as neutrophils, dendritic cells, endothelial cells and T cells.

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TREATMENT

Fusarium species frequently show resistance to antifungal drugs, which is one of the reasons why localized infections often spread into the bloodstream. To date, the pharmacological therapy with the greatest evidence against systemic fusariosis is the use of voriconazole, either alone or in combination with other drugs such as amphotericin b in its lipid formulation, this combination aims to broaden the antifungal activity against these highly resistant pathogens as they have shown an acceptable distribution either in CSF or brain parenchyma.[14] Species-specific antifungal recommendations remain elusive due to limited data. Novel antifungals nowadays appear as promising agents such as fosmanogepix and olorofim, with good CNS penetration, offering hope for future treatment options.[9]

Cytochrome P450 enzymes are important for ergosterol synthesis and virulence, important for Fusarium´s membrane function. Recent study groups are now evaluating the role of ERG5 and ERG6 for these fungi as a possible therapeutic target or to know their involvement in antifungal resistance. Also, to determine if mutations in ERG3, ERG6 and ERG11 are linked to anfotericin and azole resistance.[15]

Compressive and medullary syndromes caused by abscess or granulomas need prompt neurosurgical decompression, drainage, and resection tailored to characteristics of the lesion. In comparison with localized meningitis or radiculopathies are treated conservatively.[16] In case there is the possibility of surgical or endovascular therapy, that is, lesions such as abscesses are located in a cortical or subcortical area, not in places of greater care such as the brain stem, deep locations, or that are of multiple foci, the lesions can be removed also continuing with pharmacological therapy since it has been shown that this improves the survival of patients significantly.[4]

DISCUSSION

Even if there are a small number of species of fungi that can cause infections at the level of the nervous system, measures to prevent their proliferation must be implemented, since the neuroinfections caused by these agents can have fatal results. The problem of contaminated drug batches by *Fusarium* in previous outbreaks highlights the importance of ensuring adequate aseptic practices in the production of drugs. In addition, a hypothesis is raised about the entry route of the fungus during epidural or spinal blocks before gyneco-obstetric procedures.

General rate associated with fungal meningitis is notably high, with approximately 50% mortality rate comprising different agents, and specifically of 51% in outbreaks of *Fusarium solani.* Even though the mortality of fungal meningitis during pregnancy is not well established, given these numbers it is reasonable to infer that mortality could potentially be exacerbated by inmunological and physiological changes associated in pregnant patients.[17]

Even if the species of fungi demonstrate resistance to pharmacological therapy, it still represents the most viable alternative for contributing to patient’s outcome, in some cases during the outbreak in Mexico patients who did not receive antifungal therapy had multiple complications such as vertebrobasilar thromboses, necrosis, granuloma formation and infarcts which ended with patient´s life. Endovascular therapy faces its limitations, as they are performed based on the clinical course of the infection.[18] Voriconazole alongside lipid-based amphotericin B are considered the primary treatment option. And, finally, it is necessary to correlate the relationship between the MIC and treatment effectiveness.

While the CNS was previously considered immune-privileged, recent studies have revealed that resident cell types within the CNS, particularly glial cells, possess the capability to recognize and react to invading pathogenic fungi through pattern recognition receptors (PRRs). These responses initiate immune reactions during fungal infections. Furthermore, it has been established that immune cells can be recruited to the CNS from the bloodstream during fungal infections within this region.[19] Neutrophil-mediated drug delivery strategies offer potential applications for erradicating fusariosis, while simultaneously preserving innate immunity.

Neuroimmunological mechanisms that are implicated during an infection with *Fusarium solani* are not fully determined, in comparison with other fungal species and with other sites of infection. It is important to carry out in-depth research on the interaction at the cellular and molecular that there are new therapies that help combat such neuroinfections, specially focusing on neutrophil interaction and cytochrome activity.

Also, in order to prevent fungal neuroinfections derived from gyneco-obstetric interventions, it is crucial to follow rigorous aseptic techniques during neuraxial procedures, such as maintaining good hand hygiene, wearing sterile gloves, hat and mask, and preparing the skin with antiseptic solutions. In addition, prophylactic antifungal therapy may be considered in pregnant patients at high risk of fungal infections.

CONCLUSIONS

The crucial role of the immune system in the response to infection is emphasized, especially in how the fungus overcomes natural immunity and can reach the CNS, patient´s immune state significantly influences the outcome of the disease, being neutropenia the most negative factor. The complications associated with fungal meningitis, such as the formation of fungal aneurysms, show the severity of the disease and the importance of effective management.

Fusarium infections are challenging to treat due to drug resistance and limited therapeutic options. Pharmacological research is nowadays the most promising alternative for fighting infections caused by *Fusarium solani,* while voriconazole remains the most effective drug, novel antifungals like fosmanogepix and olorofim shows promise. Targeting enzymes involved in ergosterol synthesis, such as ERG5 and ERG6, could provide new therapeutic avenues. Neurosurgical intervention is often necessary for compressive or medullary syndromes, but conservative management is suitable for localized meningitis or radiculopathies. A combination of surgical and pharmacological treatment can significantly improve survival rates in patients with fusariosis.

Additionally, general infection control measures, such as minimizing the use of invasive devices and hand hygiene, are essential to reduce the risk of fungal infections and prevent them from becoming a cause of maternal mortality.

Fusarium solani mycoses are serious infections that can cause significant disease, especially in people with immune deficiencies. While the brain was once thought to be immune-privileged, recent research shows that resident immune cells respond to fungal infections. There still exists a big knowledge gap about how the brain responds to *Fusarium solani* infections, due to the unique environment of the CNS and technical challenges in studying it. This knowledge gap needs to be addressed to improve treatment and reduce the impact of CNS mycoses.

CONFLICTS OF INTEREST

The authors declare that they do not have conflicts of interest.

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Case Report

Clinical Case Report: Lymphedema Rehabilitation in a breast cancer patient treated with Palbociclib (Ibrance)®

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ABSTRACT

This case report describes a 64-year-old woman with a history of breast cancer who underwent a mastectomy, axillary lymph node removal, chemotherapy, and radiotherapy, and subsequently developed persistent lymphedema in her left arm. The patient received, pharmaceutical drug, Palbociclib (Ibrance®) for hormone receptor–positive breast cancer and experienced episodes of infection during follow-up. Circometry was performed to monitor changes in limb volume, and underwent complete decongestive therapy including manual lymphatic drainage, compression bandages, pressotherapy, and therapeutic exercises. Despite adherence to treatment, lymphedema was persistent and showed limited improvement over a six-month period. This case highlights the challenges of managing secondary lymphedema in breast cancer survivors and discusses the potential role of Palbociclib side effects in chronic inflammation and their possible relationship with persistent lymphedema.

Key words: lymphedema; breast cancer; palbociclib; ibrance®; decongestive therapy; case report.

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RESUMEN

El reporte de caso describe a una mujer de 64 años con antecedentes de cáncer de mama, tratada con mastectomía, extirpación de ganglios linfáticos axilares, quimioterapia y radioterapia, que posteriormente desarrolló linfedema crónico en su brazo izquierdo. La paciente estaba recibiendo Palbociclib (Ibrance®) para cáncer de mama con receptores hormonales positivos y presentó episodios de infección durante el seguimiento. Se realizó circometria para monitorear los cambios en el volumen del miembro. La paciente recibió terapia descongestiva completa, que incluyó drenaje linfático manual, vendajes compresivos, presoterapia y ejercicios terapéuticos. A pesar de la adherencia al tratamiento, el linfedema no mostro mejoria durante un período de seis meses. Este caso resalta los desafíos en el manejo del linfedema secundario en sobrevivientes de cáncer de mama y discute el posible papel de los efectos secundarios del Palbociclib en la inflamación crónica y su relación potencial con el linfedema persistente.

Palabras clave: linfedema; cáncer de mama; palbociclib; ibrance®; terapia descongestiva; caso clínico.

INTRODUCTION

Lymphedema is "a disorder of lymphostasis with protein-rich edema in which the lymph transport capacity and the proteolytic capacity of the tissues are less than normal, while the lymphatic load remains unaltered. Lymphedema is considered an evolutionary process caused by an excess of proteins, tissue edema, chronic inflammation, and excessive fibrosis".[1] "It can present as soft edema with pitting or can evolve into non-pitting edema that transforms into progressive fibrosis".[1]

Primary lymphedema is characterized by congenital or hereditary abnormalities of the lymphatic system, whereas secondary lymphedema is acquired, caused by damage to lymphatic vessels, such as trauma, cancer, or surgical interventions.[2] Lymphatic fibrosis refers to the chronic thickening of soft tissues caused by the accumulation of protein-rich lymph and the subsequent remodeling processes it triggers.[2] The lymphatic system performs two essential functions: an immunological function, involving the formation, transport, and filtration of lymphoid cells and antibodies within the lymph nodes, and a circulatory function, responsible for reabsorbing, transporting, and returning plasma proteins —such as albumins, globulins, lipoproteins, and fibrinogen— back into the bloodstream.[3]

Breast cancer treatment often involves mastectomy, axillary lymph node dissection, chemotherapy and radiotherapy. These procedures are most common to treat breast cancer, but also are very important risk factors for the development of secondary lymphedema.[4] The incidence of lymphedema among breast cancer survivor varies but it is estimated that 40% of survivors will experience lymphedema to some degree.[5] Lymphedema after breast cancer treatment is a well-recognized complication, primarily caused by axillary surgery and radiotherapy.[5] Radiotherapy can impair lymphatic endothelial integrity and function, leading to chronic disruption of drainage pathways in the lymphatic system.[5]

Palbociclib is a selective CDK4/6 protein kinase inhibitor. This protein is widely used in hormone receptor-positive breast cancer. This halts the cell cycle, stopping cells from replicating. This is important because the drugs main purpose is to block tumor growth.[6] One of its most frequent adverse effects is neutropenia, which reduces the patient's ability to control infections. Neutrophils are key regulators of the inflammatory response, and their dysfunction increases susceptibility to infectious episodes that can exacerbate lymphatic inflammation, aggravate fibrosis, and reduce responsiveness to conventional lymphedema therapies.[7]

In the clinical case presented, the patient showed impaired lymphatic function because of oncologic surgery —which included the removal of 17 axillary lymph nodes— and subsequent radiotherapy. These interventions disrupted lymphatic circulation and substantially increased the risk of secondary lymphedema. In this case, lymphedema was ultimately triggered by a mosquito bite on the affected arm, which led to local infection, chronic inflammation, and fibrotic tissue changes.

A 64-year-old female patient with a history of breast cancer, underwent a left mastectomy, axillary lymph node dissection (17 nodes removed), chemotherapy, and 30 sessions of radiotherapy. The patient subsequently underwent breast reconstruction with an expander and placement of a prosthesis. According to the patient, after five years she developed liver metastasis and was prescribed Palbociclib

(Ibrance®) on a schedule of 15 days on treatment followed by 7 days off, which she continued at the time of evaluation. She reported that her last PET-CT scan was described as "controlled," although the official oncology report was not available.

Her medical history included reactive hypertension, hysterectomy, an ovarian cyst removed three years prior, and three cesarean sections. Her family history was relevant for a father with lung cancer. Following her last radiotherapy session, she presented with shoulder discomfort and neuropathy. At the time of physiotherapy evaluation in 2019, her weight was 55 kg, height 1.60 m, and BMI 21.5.

The patient was first evaluated in physiotherapy on September 3, 2019, by a specialist in oncology and lymphedema rehabilitation. During this visit, she was instructed on lymphedema care, correct use of a compression sleeve, and post-radiotherapy stretching. She did not return to follow-up until August 13, 2024, when she presented with an edematous left arm after a mosquito bite that evolved into infection and chronic inflammation. At that time, she reported a sensation of heaviness and functional discomfort in the left arm.

Clinical examination confirmed secondary lymphedema of the left upper limb, with circometry showing increased limb volume compared to the contralateral side. Despite maintaining full range of motion, persistent edema and fibrosis were evident. Complete decongestive therapy was prescribed, consisting of manual lymphatic drainage, pressotherapy, compression bandages, and therapeutic exercises.

Between August 2024 and January 2025, the patient attended physiotherapy sessions once per week, which were temporarily increased to twice per week during exacerbations. On December 30, 2024, she confirmed continued use of Palbociclib. Despite adherence to therapy, the lymphedema showed limited improvement. On January 29, 2025, the patient expressed fatigue with the treatment and lack of significant progress. She was advised to use a compression sleeve and glove until 2:00 p.m., wear the glove alone in the afternoon, and apply nocturnal compression and self–manual lymphatic drainage as part of fibrosis management. follow-up consult was scheduled for ten days later.

In terms of lifestyle, the patient continued to engage in physical activity, with regular practice of Pilates (three to four times per week), stationary cycling, and daily domestic activities. It was also reported that the subject was carrying her two young granddaughters and walking her dogs. The clinical relevance of these activities lies in their capacity to induce repetitive physical exertion, thereby augmenting venous return in the upper limbs. It is evident that there is a close interaction between the venous and lymphatic systems. Consequently, an increased blood flow can result in an elevated lymphatic load. It is evident that, given the lymphatic system's comparatively diminished drainage capacity, this overload may precipitate the accumulation of interstitial fluid and thereby exacerbate lymphedema.

DISCUSSION

For this clinical case, the patient was assessed using circometry (see Appendix) to monitor changes in limb volume. Circometry was performed at the beginning of each session, comparing the affected arm with the contralateral side (Table 1-3).

Appendix A. Table 1 – Circometry Measurements (2019–2024)

Measurement point (cm)	R	L	L	L	L	L	L	L	L	L	L	R	R
1	16	15.5	15.6	15	15	15.4	15.3	15.4	16.2	16.4	17	15.1	15
2	17.9	17.3	16.9	16.5	16.2	16	16.4	17.7	18.3	18.7	19	15.6	16
3	20	19.9	19.8	18	19	18.4	18.5	21.1	20.7	22.5	22.5	18	17.5
4	23	22.9	22.5	21	21	21.8	22.1	22.9	24	25.5	26	20.6	21
5	25.5	14.4	24	23	23	24	23.7	25.5	26.3	27.7	28	22.8	22
*6	25.6	25.3	24.5	24	24	26	24.7	26.7	26.8	28.4	28.5	23.8	23
7	24.5	25.9	24.6	24	24	24	23.8	25.4	26.2	28.1	28	23.7	23.5
8	28.5	29	27	26	26.5	27	26.9	28	29	30.9	31	24.7	24
9	29.3	29.4	28.5	27	27	27	27.4	29.5	29.4	30.8	31	26.5	25
10	30	30.5	28.6	26.5	28	26.5	27.1	28.5	28.4	29.1	29	26.1	26.5
11	31.9	31.7	30.2	28	28	27.5	28.1	28.6	28.2	29.4	28	26.7	27
12	32.4	34.5	31	30	30	29	29.1	29.4	28.8	29.7	30	27.8	29
Hand	19	18.5	18.2	17	17.5	18	17.9	17.1	18.2	18.7	18.5	17.8	17.5
knuckles	18.2	18	17.9	16.5	16.5	16.5	18.2	17.2	17.7	18.3	18	17.1	17
fingers	5.7	5.9	5.6	5.5	5.7	5.7	6.1	6	6	6.2	6	6	6
date	3/08/19	3/08/19	7/08/19	30/08/24	9/9/24	23/09/24	30/09/24	28/11/24	3/12/24	9/12/24	9/12/24	28/11/24	9/09/24

*The highlighted data indicates when the measurements are out of range (two centimeters or more higher compared to the last session or the opposite arm)

Circometry Method:

For upper-limb measurements, 12 standardized anatomical points were used. Point 6 corresponds to the elbow crease and serves as the central reference. Measurements were taken every 6 cm proximally (toward the arm) and distally (toward the forearm) from this point. The first column of Tables 1–3 indicates these measurement points." 1 is the most distal measurement; 12 is the most proximal measurement.

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Appendix B. Table 2 – Circometry Measurements (Dec 2024–Jan 2025)

Measurement point (cm)	R	L	L	L	L	L	L	L	L	L	L	L	R
1	15.1	16.7	16.8	16.5	17.3	16.8	16.5	16	16.4	16	16.1	16.3	15.3
2	16	18.6	18.6	18.8	18.9	18.8	18.3	17.8	18.5	20	18.3	19	16.3
3	18.1	21.3	21.2	20.6	22.4	21.4	20.3	20.8	21	21.5	21.3	21.5	18
4	20.4	24.7	25.3	24.5	25.3	24.6	23.5	24.2	25	25	24.5	25.5	20.8
5	22.5	27	27.3	26.7	27.6	26.8	26.3	27.3	26.8	27.5	26.5	27.5	22.5
*6	23.5	27.5	27.8	27.7	28	27.6	27.2	27.4	27.8	28	27.6	27	23.5
7	23.	26.8	27.2	27.4	27.3	27.2	27	26.7	26.7	28	27.2	28	23
8	24.4	29.8	30	29.1	29.6	29.2	28.2	29.3	29.8	31	29.7	31.2	24.5
9	25.5	31	29.4	29.4	30.1	30	28.8	29.4	30.6	31	30	31	25.5
10	25.6	30.1	28.8	28.9	28.7	28.8	28.5	28.5	29.3	29	29.5	29.5	26
11	26.3	29.8	29	29.5	29.5	28.8	29.2	29.3	29	30.5	30.7	29.7	27
12	27	29.9	30.1	30.4	29	30.2	30	30.2	29	31	31	30	27.5
hand	17.5	18.8	17.7	18	17.4	18.1	17.5	18	17.5	18.5	18.1	18.4	18
knuckles	17.6	18.3	17.6	17.3	17.2	17.7	17.7	17.3	17.4	17.5	17.5	17.3	17
Middle finger	5.8	6.3	6.2	6.1	5.9	6.1	6.2	5.8	5.7	5.8	5.8	5.8	6
Index finger	6.1	6.6	6.4	6.3	6.2	6.2	6	6	6	6	6	6	6
thumb	6	6.4	6.2	6.5	6.2	6.3	6.1	5.9	6	6	6.7	6	6
Ring finger	-	6	5.8	5.8	5.7	5.8	5.7	5.7	5.6	5.5	5.5	5.2	5.7
Little finger	5.2	5.4	5.2	5.1	5.2	5.3	5	5	5	5.2	5	5	5.2
date	10/12/24	11/12/24	12/12/24	13/12/24	16/12/24	18/12/24	19/12/24	20/12/24	30/12/24	2/01/25	3/01/25	6/01/25	2/01/25

*R= right, L=left

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Appendix C. Table 3 – Circometry Measurements (Jan 2025 final sessions)

Measurement point (cm)	R	L	L	L	L	L	L	L	L	L	L	L	RSI
1	15.3	16.5	16.1	16.3	16	16	16.3	16.5	16.5	16.8	16.5	17	15.1
2	15.5	18	18.1	18.6	18.3	19	18.3	19	17.7	17	18	17.5	16
3	20	21	21.4	21.3	20.7	22	21	22	20.3	20.1	20.7	20	19
4	22.3	23.8	24.2	24.7	24.2	24.7	24	25	23.7	23.4	24	24	21.7
5	23	27	26	26.6	26.3	26.2	25.9	27	26.1	25.9	26	26	23.2
6	23	27.5	26.8	27	26.5	26.7	26.8	27.5	26.9	26.8	27	27	23.3
7	23	27	26.8	26.5	26.5	27.3	26.7	28	26	26.6	27	26	23.4
8	24	31	30.4	29.3	30.4	30.3	30	31	29.5	29.8	30	30	26
9	25.5	20	31	30.6	31	30.7	30.2	31	30.8	30.5	30.5	29.5	27.2
10	25	31	29.5	30.1	29.8	31	29.3	30.5	29.8	30.1	29.8	30	27.1
11	27	31	30.1	31.1	29.3	31.5	30.6	31	30	31	30.6	31	25.8
12	29.5	31	30.9	30.8	29.4	33	31.2	31.5	30.8	31.7	30.4	32.5	28.7
Hand	17	16.5	17.6	17.8	17.5	17	17.7	17.5	17.8		17.5	17.5	17.2
knuckle	17	17.5	17.1	17.6	16.8	16.5	17.4	17	17.3		17.4	17	17.5
Middle finger	6	5.5	5.6	5.7	5.6	5.7	5.7	6	5.7		5.8	6	5.8
indice	6	6	6.1	6	5.9	6	6	6	6.1		6	6	5.6
thumb	5.5	5.5	5.6	5.8	5.8	6	6	6	6		6	6	5.9
Ring finger	5.5	6.5	5.4	5.4	5.4	5	5.5	5.5	5.4		5.4	5.5	6
Little finger	5	5	5.1	5	5	5	5.2	5.5	5.1		5.1	5.2	5.4
date	8/01/24	8/01/25	9/01/25	13/01/25	13/01/25	15/01/25	17/01/25	20/01/25	24/01/25	Final de session	29/01/25	30/01/25	15/01/25

*The underlined data indicates when the measurements are out of range (two centimeters or more higher compared to the last session or the opposite arm).

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Given the persistence of lymphedema, the potential contribution of the patient's pharmacological treatment was considered. Palbociclib (Ibrance®), a CDK4/6 inhibitor used for hormone receptor–positive breast cancer, has been shown in preclinical studies to inhibit the growth of estrogen receptor–positive breast cancer cells.[8] The most common adverse events reported in randomized clinical trials include neutropenia, leukopenia, fatigue, nausea, stomatitis, alopecia, and diarrhea.[8] Neutropenia, in particular, may predispose patients to recurrent infections, which could worsen pre-existing lymphatic dysfunction. However, in this case, no laboratory data were available to confirm neutropenia at the time of lymphedema evaluation. No additional adverse effects typically associated with palbociclib —such as fatigue, alopecia, or stomatitis— were reported by the patient.

Beyond mechanical obstruction caused by radiotherapy treatment, lymphatic dysfunction significantly alters both local and systemic immunity. It disrupts immune cell trafficking and antigen transport, increasing susceptibility to recurrent infections and perpetuating chronic inflammation.[9] Persistent lymphstasis promotes fibrosis and adipose tissue deposition, further impairing drainage and creating a cycle of immune dysregulation.[9]

In this particular case, the onset of oedema was triggered by a local infection after a mosquito bite. It is well established that recurrent infection of lymphedematous tissue is a known complication, including cellulitis and other types of infection. These have been shown to exacerbate lymphatic injury and inflammation.[9] While it is established that neutrophils play a key role in host defense and tissue repair, the literature does not support a direct causal link between Palbociclib-induced neutropenia and the development of lymphedema. It is an established fact that breast cancer survivors who receive systemic therapies may experience immunosuppression and an increased susceptibility to infections. This has the potential to exacerbate existing treatment-related complications. Although there is no established correlation between neutropenia induced by systemic cancer therapies and lymphedema, impaired neutrophil function has been demonstrated to increase susceptibility to infection and may amplify local inflammatory responses.[10] This assertion is supported by immunological evidence.

CONCLUSION

To our knowledge, no studies have directly linked persistent upper limb lymphedema and fibrosis with the use of Palbociclib (Ibrance®). While Palbociclib-induced neutropenia may increase the risk of infections in lymphedematous tissues, there is no evidence to suggest that this drug initiates lymphedema or explains resistance to conventional physiotherapy. In this case, surgery and radiotherapy remain the primary contributing factors to the patient's chronic lymphedema and fibrosis. Nevertheless, immunosuppression associated with Palbociclib may contribute to a cycle of recurrent infection and inflammation, potentially aggravating the condition.

LIMITATIONS

The absence of laboratory tests and oncological records, including inflammatory markers, receptor status, and staging, is a limitation to this clinical case.

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