# Merkel cell carcinoma associated with TNF inhibitor therapy: a systematic review of case reports

Mohammed Almashali[1] MBBS SB-Derm, Manar A Alotaibi[2] MBBS, Asem Shadid[3] MBBS

Affiliations: [1]Department of Dermatology, College of Medicine, Imam Mohammad Ibn Saud Islamic University (IMSIU) Riyadh, Saudi Arabia, [2]Department of Dermatology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia, [3]Department of Dermatology, King Fahad Medical City, Riyadh, Saudi Arabia

*Corresponding Author: Manar A Alotaibi, Department of Dermatology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia, Tel: 966-505585547, Email: manaraotaibi@gmail.com*

## Abstract

**Background**: A rare neuroendocrine skin cancer called Merkel cell carcinoma (MCC) primarily affects elderly people. The objective of this study is to comprehensively review the impact of immunosuppressive medications, particularly TNF inhibitors, on the emergence of MCC.

**Methods**: PubMed, Web of Science, Science Direct, and Cochrane Library were searched. Study articles were screened by title and abstract at Rayyan Qatar Computing Research Institute, then a full-text assessment was implemented.

**Results**: A total of eight case reports with 9 patients were included. Of the total population, seven were women and only two were men. Their age ranged from 31 to 73 years. More than half the population (5 cases) were being treated for rheumatoid arthritis. All received TNF inhibitors that were associated with the induction of MCC.

**Conclusion**: We found that it is essential for physicians to explain potential cancer risks to patients before starting long-term immunosuppressive therapy and to conduct routine checks for MCC and other side effects. TNF inhibitors (infliximab, adalimumab, etanercept, and golimumab) were all associated with MCC development. Women constituted the majority of cases and most were elderly.

*Keywords: autoimmune, carcinoma, inhibitors, Merkel cell, review, systematic, TNFα*

## Introduction

Cyril Toker first presented Merkel cell carcinoma (MCC), a rare, neuroendocrine skin cancer, as "trabecular carcinoma of the skin" in 1972 [1]. Because the tumor cells resemble Merkel cells, which are found in the basal layer of the epidermis, particularly around hair follicles, the name of the condition was changed to MCC. With afferent sensory nerves and neuroendocrine properties, Merkel cells function as mechanoreceptors for light touch stimulation. These cells also express neuroendocrine markers like chromogranin-A, synaptophysin, and cytokeratin 20 [2].

Merkel cell carcinoma is a rare cutaneous neoplasm that mostly affects elderly people. There are an estimated 470 new cases of MCC each year in the United States, compared to 31,000 new cases of melanoma. Based on Surveillance, Epidemiology, and End-Results (SEER) data, Miller and Rabkin [3] determined the annual incidence as 0.23 per 100,000 for whites, which is comparable to an estimate made using the Mayo Clinic's defined patient population [4].

On chronically sun-damaged skin, MCC typically manifests as a firm-elastic, livid hemispherical tumor with a smooth, shiny surface evolving over the course of weeks to months. The fact that the tumor typically grows in a hemispherical fashion to the outside, and in an iceberg-like fashion in-depth, causing the intact epidermis to be stretched, explains the typical clinical features of MCC. Along with the more common hemispherical or nodular forms, less frequently occurring plaque-like variants can be found, especially on the trunk. Merkel cell carcinoma begins by infiltrating, but ulcerations are extremely uncommon and are only seen in extremely advanced tumors [5,6].

Early-stage satellite metastases can occur. The diagnosis is typically made based on histopathology in the majority of cases because MCC has relatively uncharacteristic characteristics [7,8]. Asymmetric dermal tumors with irregular margins and tumor cells arranged in strands or nests are how MCC presents histologically [8].

After the seventh decade of life, this type of skin cancer is more prevalent in the elderly, especially in those who have received substantial UVB exposure. It has recently been determined that MCC is related to the integration of polyomavirus DNA into the genome [9]. Another risk factor for MCC is immunosuppression. Merkel cell carcinoma has been linked to immunosuppression as a risk factor, especially in the context of HIV infection, chronic lymphocytic leukemia, and organ transplantation. Tumor necrosis factor inhibitors are immune-modulating drugs that have gained popularity in the past ten years for the treatment of inflammatory diseases like psoriasis and rheumatoid arthritis. These biological medications have been both extremely safe and successful. However, it is unknown what the long-term effects of immune modulation with TNF inhibitors will be. In particular, it is not clear whether immune modulation with biological agents carry the same risk for malignancy as long-term immunosuppression [10-13]. This study aims to systematically review the effect of immunosuppressive drugs, particularly TNF inhibitors, on developing MCC.

## Methods

This systematic review was conducted in accordance with accepted standards (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA), [14]. This was a systematic review conducted between February and March 2023.

A thorough search of four major databases, including PubMed, Web of Science, Science Direct, and Cochrane Library, was done to find the relevant literature. We restricted our search to English and took into account the unique requirements of each database. The following keywords were converted into PubMed Mesh terms and used to find the relevant studies; "Merkel cell carcinoma," "neuroendocrine carcinoma," " TNFα inhibitors," "adalimumab," "infliximab," "golimumab," "etanercept," and "certolizumab." The boolean operators "OR" and "AND" were used to match the required keywords. Publications with full English text, available free articles, and human trials were among the search results.

We considered the following criteria for inclusion in this review:

- Case reports that studied the effect of TNF inhibitors on developing MCC
- No age limits were restricted
- English language
- Free accessible articles

We used the Rayyan Qatar Computing Research Institute system to detect duplicates in the output of the search strategy [15]. The researchers used a set of inclusion/exclusion criteria to refine the combined search results to evaluate the relevance of the titles and abstracts. The reviewers carefully read each paper that met the criteria for inclusion. The authors talked about ways to resolve conflicts. The authorized study was uploaded using a data extraction form that had been created. The authors extracted data about the study titles, authors, study year, country, gender, underlying disease, drug used, drug dose, duration of drug application, time of MCC diagnosis, follow-up duration, management, and main outcomes.

To provide a qualitative analysis of the results and study components included, summary tables were created using the data gathered from the relevant studies. After the data for the systematic review had been extracted, the most efficient method for using the data from the included study articles was chosen. Studies that met the full-text inclusion criteria but did not provide data on TNF inhibitors associated with MCC were excluded.

The ROBINS-I risk of bias assessment method for non-randomized trials of treatments was used to assess the quality of the included studies [16]. The seven topics that were assessed included confounding, participant selection for the study, classification of interventions, deviations from intended

interventions, missing data, assessment of outcomes, and selection of the reported result.

## Results

A total of 300 study articles resulted from the systematic search, and 58 duplicates were deleted. Title and abstract screening were conducted on 242 studies, and 205 studies were excluded. The remaining 37 reports were retrieved and only 7 articles were not retrieved. Finally, 30 studies were screened for full-text assessment; five were excluded for incorrect study outcomes, 11 removed for unavailable data on TNF inhibitors associated with MCC, and 6 were eliminated for the wrong population type. Eight eligible study articles were included in this systematic review. A summary of the study selection process is presented in **Figure 1**.

### Characteristics of the included studies

**Table 1** includes the sociodemographic characteristics. A total of eight case reports with 9 patients were included. Two studies were conducted in the USA [17,18], two in Japan [19,20], three in Germany [21,22], one in the Netherlands [23], and one in Italy [24]. Of the total population, seven were women [17-20,22-24] and only two were men [21,22]. Their ages ranged from 31 years [17] to 73 years [23].

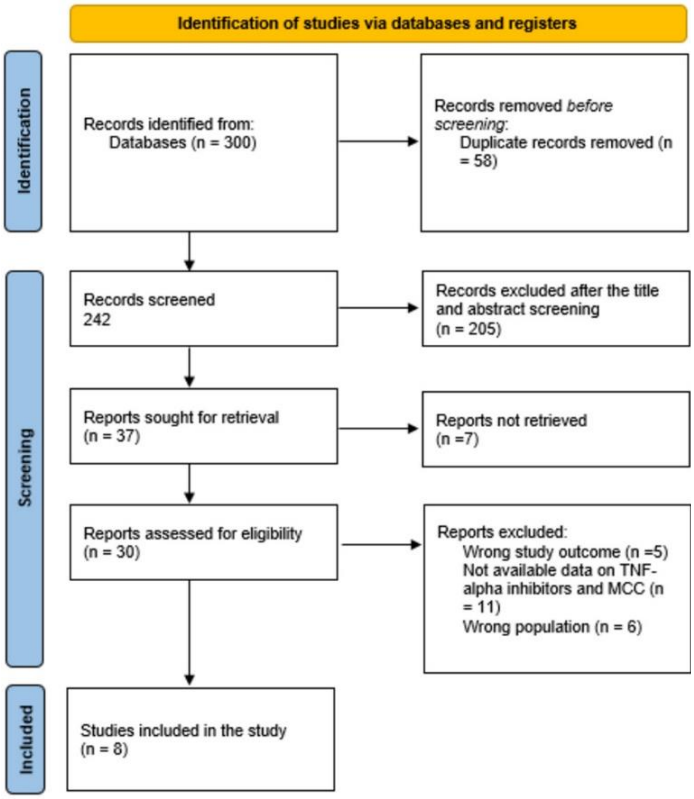


**Figure 1**. *PRISMA [14] flowchart summarizes the study selection process.*

**Table 1**. *Sociodemographic characteristics of the included participants.*

| Study | Country | Age | Gender |
|---|---|---|---|
| Harrison, et al., 2022 [17] | USA | 31 | Female |
| Delans et al., 2022 [20] | Japan | 67 | Female |
| Davenport, et al., 2018 [19] | Japan | 50 | Female |
| Hanafi, et al., 2018 [23] | Netherlands | 73 | Female |
| Kucinskiene, et al., 2014 [21] | Germany | 58 | Male |
| Linn-Rasker et al., 2012 [22] | Germany | 70 | Male |
| Linn-Rasker et al., 2012 [22] | Germany | 60 | Female |
| de Giorgi et al., 2011 [24] | Italy | 50 | Female |
| Krishna and Kim 2011 [18] | USA | 51 | Female |

Table 2 presents the characteristics of the included studies. Five cases have been treated for chronic rheumatoid arthritis [18,20,22,23], one for ulcerative colitis [17], one for Crohn disease [19], one for psoriatic arthritis [24], and one for psoriasis [21]. The reported disease duration ranged from two years to 26 years [21,22]. Four cases reported adalimumab as a therapeutic agent associated with MCC [18,20,22]; four reported infliximab [17,19,21,22], three reported etanercept [21,22,24] one reported golimumab [23]. The reported dose of adalimumab was 40mg/week [18,20], 5mg/kg every 8 weeks for infliximab [19], and 50mg/week for etanercept [24]. Infliximab was used for the longest duration, with a range from 204 [17] to 144 months [19]. Merkel cell carcinoma presented as a growing painless nodule in all the reported cases [17-24]. The follow-up duration ranged from 41 days [20] to 48 months [18]. All the included patients underwent surgical resection followed by radiotherapy, except one that was treated with radiotherapy only [19]. They reported that it is essential for physicians to explain these risks to patients before starting them on long-term immunosuppressive therapy and to conduct routine checks for MCC and other side effects. Only one study reported recurrence, metastasis, and death of the patient [22]. The development of uncommon, fatal skin tumors is one of the dangerous side effects that physicians should pay close attention to as the

use of biological therapies for chronic diseases, including TNF inhibitors.

## Discussion

To the authors' knowledge, this is the first systematic review to investigate MCC development associated with TNF inhibitors. However, our study is limited by its qualitative assessment. Interestingly, seven out of nine cases were women. This could relate to the fact that risk factors for poly-autoimmunity or the coexistence of multiple autoimmune diseases in one patient, appear to be more in women [25]. Women typically experience autoimmune disease at a younger age and with less activity than men. In women, onset typically occurs during the reproductive years and is accompanied by a rise in hormone levels. Multiple sclerosis (MS) and systemic lupus erythematosus (SLE) are two conditions in which women experience an early onset. Men have a later onset than women, which is linked to a higher prevalence of complications. Some illnesses, such as spondyloarthropathies, are more prevalent in men [26].

Eight out of the nine included patients were 50 years or older. This is consistent with the reports that stated the average patient age at the time of the initial diagnosis for MCC is around 70 years. Elderly, immunocompromised, patients with hematological neoplasms (who are typically also immunocompromised), and people with a history of other cutaneous tumors are among the population that are at risk [27]. Only one man in our survey was diagnosed with MCC at the age of 31 and he had ulcerative colitis for 17 years and was treated with infliximab therapy. In most of the cases reviewed, there was no mention of if TNF inhibitors were stopped in patients who developed MCC [18-23]. However, there were two studies that did mention adjusting the dose or stopping the TNF inhibitor [17,24].

Merkel cell carcinoma presented as a growing painless nodule in all the reported cases [17-24]. Merkel cell carcinoma manifests as a solitary, rapidly growing, cutaneous or subcutaneous tumor that typically develops on sun-exposed areas such as the head, neck, extremities, and buttocks [27,28]. However, all our included cases had nodules on extremities and only one patient had a lesion on her eyelid [20].

The development of uncommon, fatal skin tumors is one of the dangerous side effects that physicians should pay close attention to when including the use of biological therapies for chronic diseases, such as TNF inhibitors (infliximab, adalimumab, etanercept, and golimumab). TNF inhibitors have a long but mostly reassuring history of being linked to cancer [29,30]. Although the precise mechanism by which TNF inhibition may make patients more susceptible to MCC is unknown; it is hypothesized that TNF inhibitors can promote malignant growth by obstructing TNF-related anti-tumor mechanisms. The term "tumor necrosis factor" refers to a built-in mechanism that fights tumors. TNF anti-tumor properties have been effectively used to treat MCC in intralesional and limb perfusion formulations [30]. Therefore, it makes sense to hypothesize that blocking these mechanisms with anti-TNF therapy creates an environment favorable for the development of some tumors. The majority of MCCs are also believed to be caused by Merkel cell polyomavirus (MCPyV), a common human virus [30,31].

Every case that was included underwent radiotherapy after surgical resection. Several authors stated that it is critical for doctors to inform patients of these risks prior to initiating long-term immunomodulating therapy and to regularly check for MCC and other side effects. Only one study reported one patient with recurrence, metastasis, and death [23]. Merkel cell carcinomas are typically radiosensitive [32]. According to retrospective analyses, combined locoregional adjuvant radiation therapy and wide local excision can significantly lower the high local recurrence rate following surgery of the primary tumor alone [5].

Our review suggests that long-term TNF inhibitor therapy used in the treatment of autoimmune diseases may facilitate the development of a favorable microenvironment for MCC tumorigenesis. It is crucial to consider this diagnosis when assessing

immunosuppressed patients with a suspicious clinical picture, owing to the rising incidence of MCC as a whole. We think that doctors should be aware of this potential predisposition when prescribing TNF inhibitors, even though more research is required to establish a direct link between these medications and MCC.

This review is unique in which it points to the importance of discussing the potential tumorigenic side effects of TNF inhibitors. However, we included only freely-accessible, English-language articles in our study. This is known as language and publication bias, which is a prevalent limitation of systematic review study design implementation.

## Conclusion

This systematic review demonstrated that it is essential for physicians to explain these risks to patients before starting them on long-term immunosuppressive therapy and to conduct routine checks for MCC and other side effects. TNF inhibitors (infliximab, adalimumab, etanercept, and golimumab) were all associated with the incidence of MCC. Females constituted the majority of cases, and most were elderly.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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**Table 2**. *Characteristics and outcomes of the included studies.*

| Study | Underlying disease | Disease duration, Years | Drug used | Dose | Drug duration, months | MCC diagnosis | Follow-up | Treatment of MCC | ROBIN-I [16] |
|---|---|---|---|---|---|---|---|---|---|
| Harrison, et al., 2022 [17] | UC | 17 | Infliximab | NM | 204 | A nodule increasing in size on her left posterior calf that had been present for 12 months | 5 months | Wide local excision + radiotherapy | High |
| Delans et al., 2022 [20] | RA and sclerosing keratitis | NM | Adalimumab | 40mg SC, once weekly | NM | After 1-month history of a painless enlarging mass on the left elbow and intermittent fever | 41 days | Wide local excision + radiotherapy | Moderate |
| Davenport, et al., 2018 [19] | Crohn colitis | NM | Infliximab | 5mg/kg every 8 weeks | 144 | Her right lower limb had an asymptomatic nodule. After a period of 6 months, the lesion had gradually grown | 6 months | Radiotherapy | Moderate |
| Hanafi, et al., 2018 [23] | RA | NM | Golimumab | monthly injection | 6 | 3 months after a painless nodule has appeared in the upper eyelid | NM | Surgical excision + radiotherapy | Moderate |
| Kucinskiene, et al., 2014 [21] | Psoriasis | 26 | Etanercept and infliximab | NM | 12 | Rapidly growing hard subcutaneous nodus on the right arm | NM | Radical tumor removal + lymphadenectomy + local radiotherapy | Moderate |
| Linn-Rasker et al., 2012 [22] | RA | 9 | Adalimumab, infliximab, and etanercept | NM | 24 | Patient was on etanercept for 24 months years when he developed right elbow swelling | NM | Surgical excision + radiotherapy<br><br>Chemotherapy with cisplatin and etoposide for metastasis<br><br>The patient died eventually | Moderate |
| | RA | 2 | Adalimumab | NM | 7 | The patient discovered a 1.5cm×1.5cm nodule on her right upper arm 7 months after adalimumab | NM | Surgical excision + radiotherapy | Moderate |
| de Giorgi et al., 2011 [24] | Psoriatic arthritis | NM | Etanercept | 50mg/ week | 18 | A little nodule had quickly grown in size and substance and was soon associated with bleeding episodes following minor mechanical trauma in 3 months | NM | NM | High |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Krishna and Kim 2011 [18] | RA | NM | Adalimumab | 40mg/ week | NM | A painful red nodule of the upper left arm that had been developing over the preceding 1 month was the initial sign of steroid-induced Cushing syndrome | 48 months | Surgical excision + radiotherapy + systemic chemotherapy | Moderate |

NM, not mentioned; RA, rheumatoid arthritis; SC, subcutaneous; UC, ulcerative colitis.