A Preliminary Study Examining the Correlation between EGFRI Treatment, Clinic Dermatoscopy Features, and Serum Levels of Anti-Alpha-Galactosyl IgE in Colorectal Cancer Patients

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Abstract: The introduction of molecularly targeted therapies, particularly the epidermal growth factor receptor inhibitors (EGFRIs), has had a positive impact by increasing the life expectancy of patients with advanced colorectal cancer (CRC). The most used anti-EGFRIs monoclonal antagonist, Cetuximab, induces skin responses in most patients, leading to a reduction of dosages or even therapy discontinuation, all with devastating effects. Our study aimed to assess the predictive role and the possible correlations of clinical features, imaging aspects (dermatoscopy), and laboratory tests (anti-alpha-galactosyl IgE levels) for early detection of Cetuximab skin toxicity in patients with metastatic CRC. The association of IgE antibodies against goat alpha-1,3-galactose serum levels with various degrees of skin toxicity encountered during the oncologic treatment resulted in higher concentrations in patients with pruritus and hair changes. Incorporating dermatoscopy into the routine dermatological consultation allowed us to perform a severity assessment, dynamically record, and identify even the erupting lesions previously invisible to classical examination. Hence, we were enabled to generate a broad report and to classify various degrees of skin toxicity severity linked to Cetuximab treatment in 19 patients with metastatic CRC. Detecting the emergent lesions and initiating dermatological treatment in the early stages decreased the severity of skin toxicity. As a result, the duration of the antibiotic treatment was much shorter, and the risk of dose reduction or interruption of the cancer treatment was diminished. In conclusion, we emphasize the need for a regular dermatological examination with dermatoscopy of CRC patients undergoing Cetuximab treatment. Skin toxicity is a significant concern for these patients, and healthcare providers should be vigilant in monitoring and managing this side effect in order to optimize patient care. The correlation between anti-alpha-Gal IgE levels and Cetuximab-induced skin toxicities is an emerging area. More extensive studies need to be published in order to establish this relationship directly.

Keywords: colorectal cancer; skin toxicity; EGFRI; alpha-galactosyl; dermatoscopy; anti-alpha-galactosyl IgE

1. Introduction

Although numerous screening programs are currently underway, colorectal cancer (CRC) ranks third globally in terms of incidence and poses a significant mortality risk when diagnosed at advanced stages, making it the second most common cause of death worldwide [1]. Stage IV CRC accounts for 20–25% of all cases, while the survival rate...
is 15.1% [2]. Recent years have witnessed a notable rise in the use of molecular therapy among cancer patients, contributing to a marked increase in life expectancy.

The introduction of molecular therapy has been associated with an increase in life expectancy among cancer patients over recent years. EGFRIs inhibitors are classified into two categories: anti-EGFR monoclonal antibodies (Cetuximab/Erbitux, Pertuzumab/Perjeta, Panitumumab/Vectibix) and tyrosine kinase inhibitors (TKIs—Erlotinib/Tarceva, Lapatinib/Tyverb) [1]. Selecting a molecular target therapy depends on the status of the patient’s RAS (counting KRAS and NRAS) and BRAF genes. Anti-EGFRIs drugs can only be recommended when both RAS and BRAF genes are wild-type; the NCCN guidelines suggest Cetuximab or Panitumumab in this scenario [3]. The use of EGFRIs together with chemotherapy treatment is essential in patients with metastatic CRC, pancreatic cancer, non-small cell lung cancer, and squamous cell carcinoma of the neck and head [4].

Compared to classical chemotherapy, EGFRIs have a better safety profile and a better ability to target cancer cells [5].

Although systemic side effects are rarely seen in patients undergoing EGFRI treatment, most patients acquire skin toxicity during the oncological treatment [6]. Skin toxicity management plays an important role, as its occurrence frequently leads to poor compliance, dose reduction or interruption of the cancer treatment, and decreased life quality [2].

In healthy individuals, the epidermal growth factor receptor plays a major role in maintaining skin homeostasis, such as cell growth and repair processes [7], and it is normally found in the skin epidermis, eccrine and sebaceous glands, and the dendritic cells. The infiltration of the superficial dermis with inflammatory cells preferentially located in the follicular infundibulum and the presence of suppurative, abacterial superficial folliculitis were observed when using EGFRIs [8].

Characterized by a unique class of EGFRI-specific cutaneous adverse events, skin toxicity is encountered in between 45% and 100% of patients [9]. Depending on the duration of the onset of symptoms, skin toxicity can be defined as immediate rashes occurring after the first cancer treatment cycle and late skin reactions during the EGFRIs treatment. The cutaneous symptomatology starts most frequently in the first week after starting EGFRIs therapy with the occurrence of erythema and oedema, followed by the actual development of papulopustular (acneiform) eruption, then by the occurrence of skin xerosis, paronychia and hair changes (alopecia, trichomegaly, hypertrichosis), cracks, telangiectasias, pruritus, and photosensitivity [5]. The cutaneous reactions not only cause psychological and symptomological discomfort due to the changes in appearance, but also negatively influence patients’ quality of life.

Papulopustular rash, mimicking acne lesions, is the earliest and most common cutaneous adverse effect. Usually, it appears 1–2 weeks after therapy initiation and affects 50–100% of EGFRIs-treated patients, most commonly evolving 1–2 weeks after the initiation of the therapy [5,10]. The rash is formed by papules and sterile pustules located on an erythematous base that is mainly present on areas that are rich in sebaceous glands: scalp, face, anterior and posterior thorax [11,12]. Post-inflammatory hyperpigmentation spots are observed after the cessation of the treatment. Most frequently, this type of skin reaction requires the administration of tetracycline antibiotic treatment agents, ranging from 6 to 8 weeks in milder cases, and prolonged duration in severe cases [9].

According to the guidelines developed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading v5.0, there are five classes of papulopustular rash. The classification of patients into these classes allows the physician to address the cutaneous adverse events differently, to reduce the EGFRI dose, or to temporarily or permanently discontinue the EGFRI treatment in patients with grade 3 or 4 [4]. A much more accurate and detailed assessment can be made using the MASCC EGFRI Skin Toxicity Tool (MESTT), which involves counting all pustules individually. Although it gives a complete picture of the EGFRI toxicity assessment, this method is rarely used in practice. This is a consequence of the very long time it takes to complete, which may not be feasible during a routine consultation [10]. An easy to use and reliable score of the
severity of dermatological adverse events together with determining the predictive factors of Cetuximab side effects, identification of minimal skin lesions for early skin side effects detection, a valid instrument for registering additional Cetuximab side effects, and taking the required measures to prevent or treat side effects as soon as they occur to minimize its duration and impact are several crucial aspects to be established for avoiding the necessity to reduce the dosage or to discontinue the cancer treatment.

A particular category of EGFRI adverse effects of much greater severity is represented by severe hypersensitivity reactions (HSR). They can be triggered upon initiation of treatment with Cetuximab, and are mediated by pre-existing IgE antibodies \[13,14\]. Elevated IgE levels have been observed in the serum of both patients with atopy or allergies and patients with immune system abnormalities. Ongoing research shows a possible correlation between the IgE-mediated immune surveillance and the protection against tumor growth. While increased IgE levels are often associated with possible allergic reactions, current studies point towards IgE deficiency being a potential risk factor for cancer development \[15\].

Galactose-alpha-1,3-galactose(Ipha-gal) is the only oligosaccharide currently known to react with preformed IgE antibodies. This epitope is found on both Fab regions of the Cetuximab heavy chain being recognized as the focal point responsible for IgE binding \[16\]. The increased presence of these specific antibodies in the serum of patients, before receiving treatment with Cetuximab, has been correlated with the severity of hypersensitivity reactions. These reactions encompass symptoms like pruritus, laryngeal oedema, anaphylactic shock, hypotension, and myocardial infarction, as classified according to HSR CTCAE (Common Terminology Criteria for Adverse Events) \[17\].

The current study aimed to assess the predictive role and the possible correlations of clinical features, imaging aspects (dermatoscopy), and laboratory tests (anti-alpha-galactosyl IgE levels) for early detection of Cetuximab skin toxicity in patients with metastatic CRC.

2. Materials and Methods

2.1. Study Design

We conducted a prospective study on patients who had received Cetuximab between 2020 and 2022 in two of the largest oncology centers in Craiova: Sfântul Necaria and Oncolab. Patients who met the following criteria were enrolled in the study: (1) histologically confirmed colorectal adenocarcinoma; (2) advanced CRC (stage IV)—metastases determined by imaging methods or pathology exams; (3) patient underwent chemotherapy combined with anti-EGFR therapy—Cetuximab. Patients were excluded if: (1) treatment was discontinued due to disease progression or intolerance; (2) exitus occurred prematurely during treatment. The study database recorded each patient’s demographics, time of diagnosis, the existence of previous allergies, treatment history (including the number of infusions), skin toxicity generated during the Cetuximab treatment, management plan, clinical exams, lab tests.

The patients were regularly examined both clinically and dermatoscopically. Blood samples were collected at the time of clinical symptoms. The analysis enabled the investigation of a possible association between the level of IgE antibodies against anti-alpha-galactosyl and the severity of the current skin reactions.

2.2. Ethical Statements

The study has been accepted by the local ethics committee. All patients provided a written informed consent form and the study was conducted in accordance with the principles of the Declaration of Helsinki, approved by the Ethics Committee (229/20.12.2021) of University of Medicine and Pharmacy, Craiova, Romania.

2.3. Clinical Evaluation and Severity Assessment

The primary objective within the study design was to identify the oncologic patients undergoing treatment with Cetuximab, followed by complete dermatological evaluation
and identification of all cutaneous adverse effects. The additional goal was the cohort classification into severity grades according to the international standard questionnaire, MESTT.

2.4. Dermatoscopic Evaluation

For a thorough study, we introduced the dermatoscopic examination into the routine dermatological consultation, which allowed us to record and identify even the erupting lesions that were invisible to in-person visual inspection of the skin. The dermatoscopic evaluation was performed using a handheld dermatoscope (Heine Delta 30, Optotechnik, Germany) at 10× magnification with polarized light. The images were recorded using the smartphone magnetically attached to the dermatoscope. Both the areas of affected integument and the areas of healthy tissue were examined.

2.5. ELISA Detection of Anti-Alpha-Galactosyl IgE

Blood samples were collected from the patients and transported to the laboratory within 1–2 h post collection. Samples were centrifuged at 3000 × rpm for 15 min at 2–8 °C. The samples were then aliquoted and stored at −80 °C until analysis. The detection of anti-alpha-galactosyl IgE was centralized at the Human Genomics Laboratory, University of Medicine and Pharmacy of Craiova, using the BlueGene Goat galenine propeptide GAL kit, Alpha-Galactosyl IGE Human ELISA, detection range 1–25 ng/mL, with limit of detection 1 ng/mL.

We measured the alpha-galactosyl in serum using the ELISA-enzyme-linked immunosorbent assay in vitro method. Two samples were collected for each patient, one in normal concentration and one with 1/20 serum dilution.

3. Results

Our pilot study included 19 patients (3 women and 16 men) who were diagnosed with advanced CRC cancer and received Cetuximab treatment. Patient characteristics that could predict the risk of Cetuximab infusion adverse events are shown in Table 1.

Table 1. Patients characteristics.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>64.2</td>
</tr>
<tr>
<td>Range</td>
<td>49–82</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male/Female ratio</td>
<td>16/3</td>
</tr>
<tr>
<td>Provenience (Urban/Rural)</td>
<td>7/12</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>19 (100%)</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1</td>
</tr>
<tr>
<td>Former</td>
<td>13</td>
</tr>
<tr>
<td>Never</td>
<td>5</td>
</tr>
<tr>
<td>Primary site of the tumor</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>7</td>
</tr>
<tr>
<td>Rectum</td>
<td>12</td>
</tr>
<tr>
<td>History of allergies</td>
<td>0</td>
</tr>
</tbody>
</table>

All of the patients underwent chemotherapy in which 5-flourouracil, oxaliplatin, or irinotecan was combined. None of the patients had a history of allergies or atopy. Additionally, we can add that none of the patients or their families had an autoimmune or
respiratory disease. At the time of the examination, completion, and sampling, all patients (100%) had skin adverse effects.

According to the NCI CTCAE questionnaire, we classified the severity of the papulo-pustular rash as follows: 26.3% of patients with grade 1 severity, 47.3% with grade 2, 15.8% with grade 3, and 10.5% with grade 4. The patients with grades 3 and 4 required changes in the EGFRI dose.

At the time of the dermatoscopic examination, as shown in Table 2, 11 out of the 19 patients manifested developing pustules in addition to visible skin side effects. Their detection in the deep dermis allowed a more accurate assessment of the developing papulo-pustular eruptions before their clinical appearance. The 11 patients who had their pustules observed dermatoscopically were separated into two study groups. The first group, including five patients, received antibiotic treatment with doxycycline immediately after the dermatoscopic evaluation of the pustules. We then monitored the evolution of the pustules and the existing cutaneous toxicity under treatment. The second group received antibiotic treatment as a reactive treatment after the pustular eruption became clinically visible. An average time of 2.5 weeks was necessary before observing the healing of the skin lesions in patients from Group 1. On the other hand, 4 weeks of antibiotic treatment was necessary for the complete healing of the skin lesions in patients from Group 1 (Figure 1).

Table 2. Dermatoscopic features of Cetuximab cutaneous toxicity.

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Dermatoscopic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/19 patients</td>
<td>Xerosis signs</td>
</tr>
<tr>
<td></td>
<td>• Scaling</td>
</tr>
<tr>
<td></td>
<td>• White-yellow crusts</td>
</tr>
<tr>
<td>11/19 patients</td>
<td>Papulopustular rash</td>
</tr>
<tr>
<td></td>
<td>• Erythema-telangiectatic area, whitish gelatinous threads protruding out of the follicular openings</td>
</tr>
<tr>
<td></td>
<td>• Linear vessels in polygonal network, fine peripheral vessels</td>
</tr>
<tr>
<td></td>
<td>• Dilated follicles</td>
</tr>
<tr>
<td></td>
<td>• Follicular plugs</td>
</tr>
<tr>
<td></td>
<td>• Inflammatory hyperpigmentation</td>
</tr>
<tr>
<td>8/19 patients</td>
<td>Nail changes</td>
</tr>
<tr>
<td></td>
<td>• Subungual hemorrhage: well-circumscribed red dots or globules</td>
</tr>
<tr>
<td></td>
<td>• Pioigen granuloma: red discoloration with central area, irregular vessels</td>
</tr>
<tr>
<td></td>
<td>• Nail dystrophy: fine and superficial fissures, thin scales</td>
</tr>
<tr>
<td></td>
<td>• Nail fragility: horizontal splitting of the layers of the distal place</td>
</tr>
<tr>
<td></td>
<td>• Subungual hyperkeratosis</td>
</tr>
<tr>
<td></td>
<td>• Yellow and hematic serocrusts, necrotic scars</td>
</tr>
<tr>
<td>6/19 patients</td>
<td>Hair changes</td>
</tr>
<tr>
<td></td>
<td>• Black dots, yellow dots</td>
</tr>
<tr>
<td></td>
<td>• Broken hairs</td>
</tr>
<tr>
<td></td>
<td>• Short vellus hairs</td>
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<td>• Tapering hair</td>
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</table>

The serum from the 19 patients was collected once the dermatological signs and symptoms emerged. The serum assessment aimed to determine the level of anti-alpha-galactosyl IgE and the association of those antibodies, as well as the extent of skin toxicity during EGFRI treatment. Of these patients, one was excluded due to the lack of data. Two measurements were performed for each patient: a normal one and one with 1/20 dilution. The IgE specific rash ranged from 0.712 to 10.39. The assessment of the alpha-galactosyl IgE in relationship to the severity of the papulopustular rash (quantified in MESTT) indicated an irregular pattern. The patients with papulopustular rash classified as 2A and 3A showed lower values than patients classified as 1A and 2B severity stage, respectively (Figure 2).
Figure 1. The time needed for healing of skin lesions under treatment with doxycycline administered early (Group 1) versus late, after the eruption became clinically visible (Group 2).

The serum from the 19 patients was collected once the dermatological signs and symptoms emerged. The serum assessment aimed to determine the level of anti-alpha-galactosyl IgE and the association of those antibodies, as well as the extent of skin toxicity during EGFRI treatment. Of these patients, one was excluded due to the lack of data. Two measurements were performed for each patient: a normal one and one with 1/20 dilution. The IgE specific rash ranged from 0.712 to 10.39. The assessment of the alpha-galactosyl IgE in relationship to the severity of the papulopustular rash (quantified in MESTT) indicated an irregular pattern. The patients with papulopustular rash classified as 2A and 3A showed lower values than patients classified as 1A and 2B severity stage, respectively (Figure 2).

The number of patients with papulopustular rash enrolled in the MESTT grades of skin toxicity was divided as follows:
- Two patients with grade 1A,
- Zero patients with grade 1B,
- One patient with grade 2A,
- Two patients with grade 2B,
- Eight patients with grade 3A,
- Six patients with grade 3B.

Following the data correlation for the group of patients under investigation, we recorded significant alpha-galactosyl IgE changes in patients with intense and quasi-permanent pruritus, which often requires antihistamine treatment (Figure 3).

The number of patients with pruritus enrolled in the MESTT grades of skin toxicity was divided as it follows:
- Grade 1: 5 patients
- Grade 2A: 7 patients
- Grade 2B: 7 patients
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The number of patients with pruritus enrolled in the MESTT grades of skin toxicity was divided as it follows:

- Grade 1: 5 patients
- Grade 2A: 7 patients
- Grade 2B: 7 patients

Figure 3. Correlation between the alpha-galactosyl levels and the pruritus according to the MESTT scale.

Regarding the severity of hair changes, we observed a direct relationship between increased severity and the determinations of alpha-gal IgE in the serum (Figure 4). The number of patients with hair changes enrolled in the MESTT grades of skin toxicity was divided as it follows:

- Grade 0: 2
- Grade 1: 10
- Grade 2A: 4
- Grade 2B: 3

The differences between the three measured parameters of skin toxicity (scalp hair loss or alopecia/disruption of normal hair growth/increased hair changes) were statistically insignificant for each of the four MESTT grades (p > 0.05).

Figure 4. Correlation between the alpha-galactosyl levels and the hair changes according to the MESTT scale.
The differences between the three measured parameters of skin toxicity (scalp hair loss or alopecia/disruption of normal hair growth/increased hair changes) were statistically insignificant for each of the four MESTT grades ($p > 0.05$).

Several clinical findings and dermatoscopic elements regarding EGFRI related toxicity are described in Figures 5–8.

**Figure 4.** Correlation between the alpha-galactosyl levels and the hair changes according to the MESTT scale.

**Figure 5.** (A) Dermatoscopy of nail changes and chronic eczema EGFRI: sparse whitish scales, yellowish scaling (black circles), yellow and hematic serocrusts, necrotic scars (black arrow), dermatoscopic spikes/jagged edge (black arrowhead). Original magnification $\times 10$; (B) Patient with nail changes.

**Figure 6.** (A) A patient with EGFRI rash and erythmato-telangiectatic areas of the face; (B) Dermatoscopy of a EGFRI rash and erythmato-telangiectatic areas: Linear vessels, in polygonal network (black arrowhead), fine peripheral vessels (black circle), follicular plugs (black arrow).

**Figure 7.** (A) The papulopustular rash (EGFRI) dermoscopy might reveal tiny pustules before they become clinically apparent (black circle), brownish yellow areas (black arrow) postinflammatory hyperpigmentation, fine vascular pattern (black arrowheads); (B) A patient without EGFRI skin toxicity at the time of physical examination.
Figure 7. (A) The papulopustular rash (EGFRI) dermatoscopy might reveal tiny pustules before they become clinically apparent (black circle), brownish yellow areas (black arrow) postinflammatory hyperpigmentation, fine vascular pattern (black arrowheads); (B) A patient without EGFRI skin toxicity at the time of physical examination.

Figure 8. (A) Erythemat-telangiectazic area of the face observed during the physical examination; (B) Dermoscopy of typical linear vessels arranged in polygonal networks similar rosacea (black arrowheads), erythemat-telangiectazic area, whitish gelatinous threads protruding out of the follicular openings (black circle), light brown plugs surrounded by erythematous halo (black arrow).

4. Discussions

The current study aimed to provide information about the clinical, imaging, and laboratory tests (alpha-gal) of Cetuximab toxicity. Following dermatological evaluation and severity assessment, by using the handheld dermatoscope, we were able to generate a broad report and to classify different degrees of skin toxicity severity generated by Cetuximab treatment in advanced CRC patients.

Cetuximab commonly triggers an acne-like skin rash, typically appearing on the face, chest, and back in approximately 90% of patients [18] within 2–3 weeks of treatment initiation. In severe cases, reducing the dosage or stopping the therapy might be necessary.
Interestingly, the development and severity of this rash are linked to a better prognosis, causing concern for patients who might have to discontinue Cetuximab due to side effects [19]. Moreover, there are limited data available regarding preventive measures or treatments specifically for this acne-like rash, primarily extrapolated from acne treatment methods [20].

Accurate grading of the papulopustular eruption is necessary in order to determine the severity of the skin toxicity and to establish the correct dermatological treatment. Furthermore, the standardized questionnaire used in oncology trials, Common Terminology Criteria for Adverse Events (CTCAE) [21,22], is the most commonly used in medical practice. In this study, we used CTCAE, the most recent version 5.0, which allowed the assessment of papulopustular rash as grades 1–5. However, the use of the NCI CTCAE has several limitations as it is related to the surface area of the reaction and not to its severity. Although a rash is severe and mutilating, with its localization on the face, for example, it will occupy a smaller surface, disproportionately with the impact it has on the patient [4].

In this study, we noted the limitations of the NCI CTCAE questionnaire, which did not allow us to perform a complete classification and comparison in terms of the severity of skin toxicity and the serum levels of alpha-galactosyl IgE. In order to overcome the limitations and obtain a detailed analysis, we also used the MESTT grading system, developed by the Multinational Association of Supportive Care in Cancer, to be able to record all the effects of skin toxicity during the EGFRi treatment. In addition to the assessment of papulopustular rash, this method takes into consideration a wide range of criteria when assessing EGFRi-induced skin toxicity. This questionnaire shows four grades of severity of in the patients treated with EGFRi. In addition to the assessment of the papulopustular rash, we collected and assessed Information on all adverse effects generated by EGFRi: erythema, xerosis, nail and hair changes, flushing, hyperpigmentation, telangiectasias, salivation, and taste changes. We also included information about the quality of life of the patients undergoing treatment, generating a complete and comprehensive assessment. However, this is rarely used in patient assessment, as it is not feasible during a routine clinical evaluation.

The evaluation of the patients included in our study was performed periodically to assess both immediate and late cutaneous adverse effects of EGFRi treatment. Such late effects include pruritus and skin xerosis, which occur 2–3 months after the treatment initiation and are present in about 35% of patients. Clinically, xerosis often has the appearance of atopic dermatitis and can lead to the formation of eczema craquele. In terms of pruritus, secondary bacterial infections or extremely painful cracks may occur following scratching lesions [23,24]. Hair changes occur later than 1–2 months after the initiation of the EGFRi therapy and they consist of localized hair loss or morpho-functional changes in hair color and structure, with the hair becoming wavy and curly. The eyelashes may also lengthen, become curly (trichomegaly), and may cause blepharitis, keratitis, or conjunctivitis. Other changes include loss of pigment in the eyelashes with subsequent appearance of white hair [6,25,26]. Nail changes are diverse and include: paronychia, pyogenic granuloma, cracked lateral nail folds, pitting, and swelling. The nails are very thin, brittle, and show onycholysis phenomena, sometimes with complete detachment of the nail from the nail bed [6,27–30].

By integrating dermatoscopy into current practice, it is possible to identify structures at a submacroscopic level, changes that cannot be identified without the help of a device [31], which, in some cases, can place the patient in a lower severity grade. To the best of our knowledge, this is the first study evaluating the clinical benefit of integrating dermatoscopy into current practice in cancer patients treated with EGFRi. We introduced the dermatoscopic examination into the routine dermatological consultation in our study to reach a greater accuracy during the dermatological examination. This addition allowed us to record and identify even the erupting lesions that were previously invisible during the classical inspection. The fact that this dermatoscope was portable allowed the evaluation of patients directly in the oncology center where they were undergoing EGFRi treatment. The device enabled us to completely and thoroughly highlight and record all EGFRi cutaneous
adverse effects, as well as their classification into different degrees of severity. The early identification of lesions and the dermatological treatment initiation in the early stages ameliorated the severity of skin toxicity. Consequently, we consider the use of dermatoscopy as being a useful tool in the clinical setting.

As there is no guideline on the standard treatment for EGFRI-induced skin toxicity, the treatment of the cutaneous adverse effects of EGFRI is managed differently: prophylactically or reactively. In the case of the pustules identified early with the dermatoscope, before they became clinically present, the immediate administration of antibiotic treatment stops the developing rash and improves existing skin signs. The administration duration of the antibiotic treatment has a much shorter interval.

According to the study by Beech et al., the development of grade 2 or higher skin toxicity occurs over 2–3 weeks. The use of the reactive treatment provides time to manage pre-existing reactions and prevents the development of higher degrees of severity, highlighting the usefulness of the reactive versus the prophylactic treatment [10].

The use of EGFRI has increased considerably due to the much-reduced systemic effects compared to classical chemotherapy. A classic mAbs adverse effect is the triggering of hypersensitivity reactions (HSR), which most commonly can occur with the first infusion. Numerous studies highlight the triggering of hypersensitivity reactions as being related to the pre-existence of specific IgE antibodies [32–34]. It is already known that some people are more likely to develop IgE antibodies against galactose-α-1,3-galactose after being naturally exposed to galactose-α-1,3-galactose. The presence of IgE antibodies against galactose-α-1,3-galactose before treatment may put patients receiving this type of monoclonal antibody at risk for HSR [16]. In our study, the irregular variation of the alpha-galactosyl IgE in relation to the severity of the papulopustular rash might be related precisely to the pre-existence of specific IgE antibodies. The employment of tests that reveal anti-Cetuximab IgE levels would allow a better selection of candidate patients for treatment with this monoclonal antibody [35].

No drugs have been found to prevent the onset of HSR following the Cetuximab administration. However, the use of corticosteroids prior to the initial Cetuximab infusion in patients with elevated alpha-galactosyl has been shown to decrease the risk of anaphylaxis [36]. Both the HSR reactions and the cutaneous adverse effects occurring during the EGFRI treatment are important to be addressed. Similarly to the HSR reactions, further skin toxicity in advanced grades can lead to the discontinuation of the cancer treatment or even to the death of the patient.

The importance of cutaneous adverse effects and the massive impact they have on the patients’ lives led us to look at the alpha-galactosyl IgE serum values in patients with different degrees of skin involvement. Subsequently, we investigated whether these levels can be correlated with the degree of severity of the existing skin toxicity.

The identification of possible markers for early detection of EGFRI-therapy-induced cutaneous adverse effects and their correlation with severity is a hot topic in recent studies. To date, alpha-Gal detection has been used to assess HSR effects that might be triggered during the first EGFRI infusion, or, very rarely, at subsequent infusions. In addition to its role as a predictive marker of HSR, in our study, we determined its importance in terms of correlation with adverse skin reactions triggered during the Cetuximab treatment. Part of this study focused on identifying the role of alpha-Gal in patients with skin involvement during EGFRI treatment and highlighting possible correlations with skin toxicity severity grades. Identifying triggers in this matter could facilitate a good management of skin toxicity and prevent the onset of severe adverse effects, which can sometimes lead to death of the patients. In the study group, alpha-Gal levels were correlated with these EGFRI-therapy-induced cutaneous adverse effects. Among the most important correlations, it was possible to identify the direct association between the level of alpha-Gal and the intensity of pruritus, especially the quasi-permanent pruritus requiring antihistamine administration. In addition, patients with hair changes showed reactions that were directly proportional to increased alpha-Gal levels. Currently, there is no guideline on the management of EGFRI-
induced skin toxicity. The early identification of elevated alpha-Gal levels and the initiation of prophylactic dermatological treatment may represent an important line of research in the treatment of patients with skin involvement, perhaps representing a starting point for the development of a standardized guideline, so necessary in the daily practice regarding the EGFRI patients.

According to Lungulescu et al., a total of six studies assessed the diagnostic accuracy of the anti-IgE for galactose-\(\alpha\)-1,3-galactose in patients with HSRs to Cetuximab. The meta-analysis concluded that more studies are needed to establish a protocol necessary for the proper prediction and avoidance of HSR related to Cetuximab [32]. Hence, we consider that the theme of the paper is important and interesting, even though it might seem to be without great novelty.

The early identification of lesions and the initiation of the dermatological treatment in the early stages stopped the severity of skin toxicity and the duration of the antibiotic treatment was much shorter, with reduced effects on the human microbiome, as shown in one of our previous studies [37].

Regarding the novelty of the current paper, to the best of our knowledge, this is the first study evaluating the clinical benefit of integrating dermatoscopy into current practice in cancer patients treated with EGFRI, in addition to the correlation between alpha-galactosyl IgE serum values and cutaneous toxicity. However, several limitations must be acknowledged. Firstly, one of our study limitations is that we lacked a group of patients who received Cetuximab without developing skin toxicity or a group control of patients without CRC. Overall, the number of patients included in the study was limited, mainly due to the general low number of patients treated with EGRFI, specifically Cetuximab, in our region; the short lifespan of patients with advanced or metastatic cancer treated with EGFRI; and also the dynamic of the follow-up of the patient from initiation, detailed dermatological consultation, and complete registration of all data in databases, completion of all questionnaires, considering also the COVID pandemic context. Another drawback of our study is the lack of preliminary testing of the specific IgE antibodies, before the initiation of Cetuximab protocol and several times during the oncologic treatment. It would have offered a more complex overall image of the patient’s risks of developing adverse events. All in all, a more accurate study design should imply: (1) obtaining serum samples of alpha-galactosyl IgE from a control group without CRC, autoimmune disease, and atopic personal or family history; (2) samples of serum alpha-galactosyl IgE collected at several moments during the study: before the initiation of Cetuximab protocol, 2 weeks after introducing the patient to Cetuximab (when skin lesions start to unveil), at the time of treatment completion, and at any time after finishing the treatment, when and if late Cetuximab side effects appear; and (3) the simultaneous assessment of each patient’s clinical status with the MESTT grading system and dermatoscopy exam in relation to serum alpha-galactosyl IgE levels. These are the three essential conditions for correlating serum levels of alpha-galactosyl IgE with the possible emergence of skin side effects or with the severity of Cetuximab skin toxicity.

Given the fact that individuals facing Cetuximab-induced skin toxicity tend to exhibit better response rates and derive more advantages from Cetuximab treatment, recognizing and diagnosing skin toxicities early can significantly enhance patient management. Consequently, identifying patients at a higher risk of experiencing Cetuximab-induced skin toxicity becomes more valuable [38].

5. Conclusions

The early identification and diagnosis of Cetuximab-induced skin toxicity plays an important role not only in improving the quality of life of these patients, but also in avoiding severe skin adverse effects, leading to dose modifications, discontinuation of cancer treatment, or even death. The need for a complete and regular dermatological examination of these patients is, thus, emphasized. The correlation between anti-alpha-Gal
IgE levels and Cetuximab-induced skin toxicities is an emerging area. More extensive studies need to be published to directly establish this relationship.

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**References**


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