Consensus Document on the Evaluation and Treatment of Moderate to Severe Psoriasis. Spanish Psoriasis Group*

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Abstract. The treatment of psoriasis has been revolutionized by the introduction of biologic agents; these agents achieve skin clearance and long-term improvement without the risk of toxicity that has limited use of the traditional systemic treatments. The role of systemic treatment in the management of psoriasis is being reviewed on the basis of a large volume of scientific evidence on the efficacy and safety of biologic agents, and new therapeutic goals and strategies are being devised for patients with moderate to severe psoriasis. This has led to the need to establish severity criteria that will provide the rationale for the indication of the different systemic agents currently available for the treatment of moderate to severe psoriasis, as well as therapeutic goals, efficacy measures, therapeutic strategies, screening protocols, and choice of treatment based on the risk-benefit ratio of the different agents. These criteria must be established through consensus by experienced dermatologists and based on available scientific evidence. The present document reflects the consensus of the Spanish Psoriasis Group on these different issues in the management of moderate to severe psoriasis.

Key words: psoriasis, treatment, consensus, criteria, biologic agents.

Introduction

Psoriasis is a chronic recurrent skin disease that affects 1.4% of the Spanish population. 1 Although the cutaneous manifestations of psoriasis are only life-threatening in...
### Severity Criteria

The measures normally used to assess the severity of psoriasis in dermatological practice are the proportion of the body surface area (BSA) affected and the Psoriasis Area and Severity Index (PASI). It is generally accepted that patients with a greater than 5% affected BSA have moderate to severe psoriasis and in most recent clinical trials a PASI above 10 or 12 has been used as an inclusion criteria to define moderate to severe psoriasis. An affected BSA greater than 10% and a PASI score of 12 or higher have been proposed as criteria for severe psoriasis for use in clinical trials.

While some authors define moderate psoriasis as a PASI between 7 and 12 and severe psoriasis as a PASI higher than 12, others prefer to use the “rule of tens” criteria, which define severe psoriasis as a PASI higher than 10, an affected BSA of more than 10%, or a Dermatology Life Quality Index (DLQI) score greater than 10.

When using quality-of-life indices to assess psoriasis, clinicians should remember that, even when an instrument has been validated, cultural differences exist that limit the validity of a least some of the tools currently available. Consequently, we need to develop new instruments for measuring quality of life specifically in patients with psoriasis and to validate them and establish the sensitivity of their response to the effects of therapeutic interventions.

The use of objective scales, such as the PASI and the BSA, is essential for assessing disease severity before starting systemic therapy and to facilitate subsequent assessment of response to treatment. These instruments are also essential for correctly assessing treatment response in the context of clinical trials. However, in many cases the results of scales alone are inadequate for defining severity from the standpoint of the patient’s needs.

The criteria of prior hospitalization, which has been proposed as an indicator of severity, is highly dependent on each country’s healthcare system (availability of beds, willingness to be hospitalized, etc) and would not, in general, be a very useful criteria in Spain. In the definition of psoriasis disease severity and the decision to use either conventional or biologic systemic treatment, factors other than the extension and severity of the lesions must be taken into account. Other cases of psoriasis that are considered severe include those involving special forms of the disease known to have a more aggressive course (pustular, erythrodermic, etc), cases that fail to respond to topical treatment, and those in which the disease affects...
It should be remembered that the “rule of tens” criteria for severity was used in clinical trials in which the participants had not recently received any treatment (“therapeutic wash out”). When none of the therapeutic objectives described below are achieved in a patient receiving systemic treatment, the patient should be considered a candidate for a change of medication or biologic therapy even when the objective scores (BSA, PASI, and DLQI) are lower than those specified above.

### Indication for Systemic Treatment

Systemic treatment is indicated in patients with psoriasis in the following situations: a) disease not controlled with topical treatment; b) extensive disease (BSA >5%-10%); c) PASI >10; d) rapid worsening; e) involvement of visible areas; f) functional impairment (palmo-plantar or genital involvement); g) subjective perception of severity (DLQI >10); h) extensive erythroderma or pustular psoriasis; and i) disease associated with psoriatic joint disease.

### Treatment Objectives

The objective of treatment is satisfactory therapeutic control of psoriasis, and the ultimate goal (ideal outcome) is sustained complete clearance (PGA = 0) or almost complete clearance (PGA = 1) or, when this is not possible, a minimal localized area of affected skin that can be controlled with topical treatment (PG = 2, PASI <5). With the help of biologic agents, it is now reasonable to expect to achieve this objective in a significant percentage of patients since these new treatments are free from the acute toxicity and cumulative dose-dependent and organ-specific toxicity that makes it difficult to achieve this objective with conventional systemic therapy.

In terms of quality of life, the treatment objective should be to achieve a DLQI of 0 or 1, which indicates that the disease is not affecting the patient’s quality of life. 

The minimum threshold of efficacy required would be a DLQI <5, which indicates that the effect of the disease on the patient’s quality of life is slight.

In practice, for most patients the treatment objective can be defined in terms of a percentage of relative improvement in PASI after a predetermined interval (for example, 3 or 6 months). With the biologic agents currently available and the new agents still undergoing clinical trials, a reasonable treatment objective should be to achieve a PASI 75 response (within 10 to 16 weeks) and an optimal response would be a PASI 90 response (equivalent to an absence of signs and symptoms, that is, clearance (PGA = 0) or only minimal signs of disease (PGA = 1). This standard would be equally applicable to
conventional systemic treatments with comparable rates of response. A PASI 50 response is considered to be the lowest acceptable threshold of efficacy after 3 months. Physicians should always try to achieve and maintain a PASI 75 response unless the patient considers the response obtained sufficient.

The treatment objective should be one of the following: PASI 75 (≥ 75% improvement from baseline PASI), PASI <5, PGA ≤1, or DLQI <5.

New instruments are needed to assess quality of life, and new studies are required to establish which of the domains of the available instruments (general, dermatological, or psoriasis specific) best reflect changes in response to treatment.

Definition of Treatment Failure

Response to treatment should be assessed continuously during treatment and at 3 to 4 months. Lack of response or treatment failure is defined as follows: a) failure to achieve a 50% reduction in PASI from baseline or loss of such a response; or b) continuing to have a PASI greater than or equal to any of the scores specified above as criteria for moderate to severe psoriasis; or c) any response considered inadequate by both the physician and the patient.

Treatment failure is an indication for changing treatment or prescribing a combination regimen.

Definition of Loss of Response

Loss of response is defined as a failure to fulfill the therapeutic objective at any time during treatment, judged either on the basis of objective parameters (typically failure to sustain the 75% improvement from baseline PASI, that is, the PASI 75 response) or in the opinion of both the patient and the physician.

Loss of response may take the form of a transient exacerbation that can be controlled by adjusting the dosage regimen (dose and frequency of administration) or by prescribing combination therapy (adding topical medication, ultraviolet light B (UV-B) phototherapy, acitretin, methotrexate, or cyclosporine) particularly when the patient is being treated with biologic agents.

Definition of Relapse, Remission, and the Rebound Effect

It is important to establish definitions that allow us to describe the duration of the therapeutic effect of treatment in the context of both clinical trials and normal clinical practice.

Relapse (after withdrawal of effective treatment) is defined as a greater than 50% reduction in the maximal improvement from baseline obtained with treatment (for example, if the PASI was 14 at the start of treatment and 2 when treatment was discontinued, a PASI of 8 or higher would constitute a relapse).

The interval between withdrawal of treatment and relapse is called the period of remission or the duration of therapeutic effect.

The term rebound effect refers to either a deterioration of the psoriasis equivalent to at least 125% of the baseline PASI occurring within 3 months of withdrawal of treatment, or a morphological change (the onset of generalized erythrodermic or pustular psoriasis).

Treatment Regimen

The acute or cumulative adverse effects associated with conventional systemic treatment have traditionally led to the use of cyclical regimens and case-by-case selection of medication based on the characteristics and comorbidities of each patient (age, the possibility of conception, alcoholism, obesity, dyslipidemia, hypertension, liver disease, etc). These side effects have also justified the use of rotational therapy, which takes the form of alternating cycles of treatment with different drugs, but in general each patient has an ideal response to a particular drug and some patients have comorbidities or risk factors that limit the range of drugs that can be used. When biologic agents are used, this problem does not exist and the choice of treatment depends principally on the intrinsic characteristics and past history of the disease (need for treatment, etc).

When assessing the indication for biologic treatment in routine practice, a number of factors should be taken into account in addition to the baseline PASI (or alternative assessment using any other severity scale, such as the BSA, PGA, or DLQI). These additional factors include the lack or loss of response to systemic treatment, the patient’s intolerance or contraindication to other systemic treatments, as well as the stability or instability of the inflammatory component of the disease (erythema, pain/pruritus) and the rate of deterioration of the current flare. Unstable disease will determine the choice of a treatment known to have a rapid onset of action, whereas stable psoriasis can be treated with a range of different therapies.

Today, the clinician’s chief dilemma when prescribing biologic agents is whether to choose continuous (as long as response is sustained) or intermittent (pulse) treatment.
Candidates for Continuous Therapy

1. Patients with a prior history of sustained disease activity involving 1 or more flares during at least 6 months a year in whom treatment has failed to produce a satisfactory level of control or has been curtailed because of contraindications and/or adverse effects.
2. Patients who show a good response to therapy, but who are highly dependent on treatment because of early recurrence (relapses within 2 months or less).
3. Patients in whom loss of response has important psychological repercussions or a significant impact on quality of life.
4. Patients with joint involvement.
5. The presence of comorbidities associated with an increased risk of cardiovascular disease could be a factor to consider in the decision to prescribe continuous treatment.

Biologic agents are the drugs best adapted to a continuous treatment regimen. Owing to their cumulative toxicity, traditional systemic treatments are more suitable for intermittent or rotational treatment regimens.

Candidates for Intermittent Treatment

Patients with a history of exacerbations of short duration with 1 or more flares during less than 6 months a year.

Criteria for Retreatment

Patients who have experienced complete clearance perceive relapse and loss of response quite differently than those who have not experienced clearance for a long time. The negative impact of a particular PASI score on the quality of life and psychological perception of those in the latter group is greater. In such cases, an absolute PASI score above 5, a DLQI of more than 5, or a PGA of at least 3 can be, depending on the case, a reasonable criteria for retreatment.

In the case of a relapse or because of a decision taken jointly by the patient and physician, retreatment with the same agent can be considered or alternatively with a different form of therapy if the circumstance or preferences of the patient have changed.

Transition Between Treatments

Unlike the procedure used in clinical trials (abrupt withdrawal of treatment followed by a washout period), in normal clinical practice the treatment being withdrawn can be continued throughout a transition period when followed by a biologic agent with a slow onset of response or may be withdrawn abruptly when replaced by a biologic agent with a faster onset of effect, such as infliximab and possibly adalimumab.

When changing a patient’s systemic therapy (whether conventional or biologic) because of adverse effects or lack of efficacy, a number of transition strategies can be used depending on the judgment of the physician. These include overlapping the old and new treatments, substitution without continuity, or using an overlapping traditional treatment to cover the transition between 2 biologic regimens.

Combination Therapy

Although combining different therapies is not generally recommended, the combination of topical treatments with biologic agents is often used to increase the rate of response or improve response in the case of localized lesions and to control temporary flare-ups.

Combinations of systemic treatments—including photochemotherapy—with biologic agents can be prescribed (using doses that minimize the risk of side effects) for limited periods of time to prevent a relapse after withdrawal of a systemic treatment, before the onset of the therapeutic effect in the case of certain biologic agents, to accelerate response at the beginning of a course of biologic treatment, to improve therapeutic response to these agents, to control temporary flares, to serve as a transition between biologic treatments, and when treatment is withdrawn because of treatment failure or other causes.

Pretreatment Screening

A complete medical history including the following information should be obtained for all patients with psoriasis who are candidates for systemic treatment: duration of the disease, prior systemic treatments and hospitalizations, presence or absence of arthropathy, history of infectious diseases and possible exposure to tuberculosis, history of past illness, concurrent medications, comorbidities, and the presence of any contraindications or risk factors for adverse effects.

Following a preliminary discussion with the patient concerning the safety, efficacy, and method of administration of the treatment, a quantitative baseline assessment should be performed to determine disease severity (PASI, BSA, PGA, DLQI) and a standard laboratory workup including both complete blood count and biochemistry should be ordered.
When considering the prescription of conventional systemic treatment or photochemotherapy, the contraindications and possible side effects shown in Table 1 should be taken into account. When treatment with a biologic agent is being considered, the medical history obtained should include the following information: duration of the disease, prior systemic treatments and hospitalizations, presence or absence of arthropathy, history of infectious diseases and possible exposure to tuberculosis, the

Table 1. Contraindications and Possible Adverse Effects of Conventional Systemic Therapy and Photochemotherapy That Must be Taken into Account

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Phototherapy</th>
<th>PUVA</th>
<th>Acitretin</th>
<th>Methotrexate</th>
<th>Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xeroderma pigmentosum, systemic lupus erythematosus, heart failure or ischemic heart disease (orthostatic), claustrophobia</td>
<td>Photostvability, squamous cell carcinoma and possibly melanoma, breastfeeding or pregnancy (category C), aphakia, immunosuppression, heart failure or ischemic heart disease (orthostatic), claustrophobia</td>
<td>Pregnancy (category X), breastfeeding, teratogenicity makes contraception necessary during treatment and for at least 2 to 3 years after treatment</td>
<td>Pregnancy (category X), breastfeeding liver disease, alcoholism, immunodeficiency, chronic renal failure</td>
<td>Renal failure, hypertension, neoplastic disease, infections, immunodeficiency, concomitant treatment with PUVA, UV-B, or coal tar Pregnancy (category C) or breastfeeding</td>
<td></td>
</tr>
</tbody>
</table>

| Principal toxic effects | Burns, presumed increased risk of skin cancer, premature skin aging | Burns, premature skin aging, increased risk of melanoma and non-melanoma skin cancer, possible eye damage | Fetal death and/or abnormalities, hepatotoxicity | Fetal death and/or abnormalities, myelosuppression, hepatotoxicity, pneumonitis, stomatitis | Nephrotoxicity, hypertension, immunosuppression (increased risk of infection and neoplastic processes) |

| Other common adverse effects | Nausea | Hair loss, dry lips, cheilitis, dry or sticky skin, hyperlipidemia | Nausea, anorexia, fatigue, headache, hair loss | Hypertrichosis, gingival enlargement, gastrointestinal intolerance, neurological abnormalities, abnormal lipid profile, hyperglycemia, hyperuricemia, hyperpotassemia, hypomagnesemia |

Abbreviations: PUVA, psoralen + ultraviolet A treatment; UV-B, ultraviolet B phototherapy. Adapted from Menter and Griffiths. The points that are typically the most important are highlighted in bold face.

1. When considering the prescription of conventional systemic treatment or photochemotherapy, the contraindications and possible side effects shown in Table 1 should be taken into account. When considering the prescription of conventional systemic treatment, physicians may also decide to order the following tests: antinuclear antibodies, chest radiograph, Mantoux test with 2 tuberculin units (TU) of purified protein derivative (PPD)-23, and blood tests for human immunodeficiency virus, hepatitis B and C virus.

2. When treatment with a biologic agent is being considered, the medical history obtained should include the following information: duration of the disease, prior systemic treatments and hospitalizations, presence or absence of arthropathy, history of infectious diseases and possible exposure to tuberculosis, the...
presence of comorbidities and possible risk factors for side effects and/or contraindications, history of past illness (with particular emphasis on congestive heart failure, lupus erythematosus, and demyelinating disease, including any possible family history), and concurrent medication.

To rule out latent tuberculosis infection, a chest radiograph and a TB-focused medical history including all the pertinent questions should be obtained. If treatment with a tumor necrosis factor (TNF) α inhibitor is contemplated, a tuberculin skin test should be performed with 2 TU of PPD-23. When the skin test result is negative, the test should be repeated between 7 and 15 days later (to eliminate any confusion due to a booster effect). This two-step testing is particularly important in patients who could be anergic, such as those over 65 years of age and patients receiving treatment with methotrexate, cyclosporine, or other immunosuppressants. The tuberculin skin test is considered positive when the diameter of the induration is at least 5 mm at 72 hours. Even when they do not have radiographic abnormalities, patients with a positive skin test result should follow a course of prophylactic chemotherapy with isoniazid 300 mg/d. While it is generally recommended that chemoprophylaxis should be started 1 month before start of treatment with anti-TNF agents, the minimum necessary interval is unknown and a shorter interval is probably sufficient or it may even be enough to start both treatments simultaneously.21 The prophylaxis should be taken for the full 9 months (unless another regimen is used in line with local practice). Alternatively, these patients may be candidates for treatment with efalizumab.

Selection of Conventional Systemic Treatment

In addition to the contraindications, side effects, interactions, and special precautions regarding use described above, all of which influence the choice of drug, clinicians should also take into account the efficacy-related information summarized in Table 2.18,22-25

### Indication for Biologic Treatment

Biologic agents are indicated for the treatment of moderate to severe psoriasis (as defined above) in adult patients who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including phototherapy, photochemotherapy, or other biologic agents. Intolerance may be due to side effects or toxicity, whether acute or due to the cumulative dose.

This definition includes the following patients:

1. Patients in whom effective control is not achieved with the available systemic agents, in monotherapy or combination regimens.
2. Patients in whom relapses occur rapidly, that is, less than 3 months after withdrawal of any type of treatment.
3. Patients who require high doses of conventional systemic therapies (with the risk that entails of adverse effects due to acute or cumulative toxicity in a substantial percentage of patients).
4. Patients who are intolerant to some systemic therapies (who experience toxicity or adverse reactions with effective doses) or have a high risk of cumulative toxicity with methotrexate, cyclosporine, acitretin, or photochemotherapy even when laboratory test results are normal. The risk of toxicity may be due to the dose required, the duration of treatment, individual susceptibility, or to individual risk factors, such as age, sex, comorbidity, and potential drug interactions.
5. Patients who are not good candidates for treatment with photochemotherapy because of their work, daily schedule, travel requirements, or availability.

The efficacy data available from the clinical trials does not allow us to differentiate between patients in

### Table 2. Efficacy-Related Information for Traditional Systemic Treatments

<table>
<thead>
<tr>
<th></th>
<th>Acitretin</th>
<th>Methotrexate</th>
<th>Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard dose regimen</strong></td>
<td>0.3-0.5 mg/kg for 4 weeks, subsequent increase</td>
<td>5-20 mg/wk</td>
<td>2.5-4 mg/kg (maximum 5 mg/kg)</td>
</tr>
<tr>
<td><strong>Onset of clinical effect usually occurs within</strong></td>
<td>4-8 weeks</td>
<td>4-8 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Efficacy: PASI 75 at 8-16 weeks</strong></td>
<td>Highly variable and difficult to establish: 25%-56%</td>
<td>25%-60%</td>
<td>50%-70%</td>
</tr>
<tr>
<td><strong>Efficacy: PASI 90 or clearance at 8-16 weeks</strong></td>
<td>9%</td>
<td>11%</td>
<td>13%-50%</td>
</tr>
</tbody>
</table>

Adapted from references 18, and 22 to 25.
whom biologic therapy is indicated because of a lack of response to conventional systemic therapy and those who are candidates because they are intolerant to or have contraindications to the doses of conventional systemic treatment required to achieve a satisfactory response. These 2 subgroups of patients may have different therapeutic needs, and these needs might even determine the choice of biologic agent.

All the biologic agents approved for the treatment of psoriasis must be made available to all patients who are candidates for such therapy, without unnecessary delay or any type of limitation representing inequitatble treatment.

Biologic agents should be prescribed by dermatologists with broad experience in the treatment of psoriasis with traditional systemic agents and biologic agents, and the severity of the patient’s condition must be objectively documented before, during, and at the end of every course of treatment in order to assess the efficacy of treatment in every patient.

### Selection of Biologic Therapy

As well as any potential contraindications, side effects, and special precautions for use discussed above that determine the choice of drug, the efficacy-related information shown in Table 3 should also be taken into account.18,25-33

| Table 3. Efficacy-Related Information for Biologic Agents18,25-33 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Efficity: PASI 75 at 10-16 weeks** | **Efalizumab** | **Etanercept** | **Etanercept** | **Etanercept** | **Infliximab** |
| Onset of clinical effect usually occurs within: | 4-8 weeks | 4-8 weeks | 4-8 weeks | 4-8 weeks | 1-2 weeks |
| Efficacy: PASI 75 at 10-16 weeks | 22%-39%, 12 weeks | 30%-34%, 12 weeks | 49%, 12 weeks | 38%, 12 weeks | 80%, 10 weeks |
| Efficacy: PASI 90 at 10-16 weeks | No data | 11%-12%, 12 weeks | 21%-22%, 12 weeks | 14%, 12 weeks | 57%, 0 weeks |
| Efficacy: PASI 90 at 24 weeks | No data | 20%-21% | No data | 42% | 58% |
| Duration of remission, (median)24 | 84 days | 70-90 days | No data | 140 days after induction | No data |
| Long-term treatment: Response sustained | Response sustained; studies with different doses (50 mg/wk, 50 mg twice weekly) | No data available | 61% PASI 75; 45% PASI 90; at week 50 | 87% PASI 75; 63% PASI 90; at 18 months |
| Most commonly reported adverse effects | Flu-like symptoms, high white blood cell and lymphocyte counts | Injection site reactions | Infusion reactions | Injection site reactions |
| Chief risks* | Exacerbation or rebound of psoriasis, thrombocytopenia | Tuberculosis and other infections | Tuberculosis and other infections | Tuberculosis and other infections |

*Guidelines have recently been published on the subject of treatment monitoring and the use of vaccinations in patients treated with biologics for psoriasis.24

Abbreviations: iv, intravenous; sc, subcutaneous.

Adapted from references 18 and 25 to 33.
None of the biologic agents should be considered generally preferable to the others in the treatment of moderate to severe psoriasis on the basis solely of response rates published in clinical trials. Instead, the choice of a biologic agent should be made on a case-by-case basis for each patient taking into account the available information and recommendations.

The choice of biologic treatment should be made in each case taking into account the following considerations:

1. **Patient-related factors**, such as the presence of concomitant disease, psoriatic arthropathy, comorbidity, weight, and the risk of possible adverse effects.
2. **The disease characteristics** including the following: a) the case history (prior treatment, speed of relapse after treatment, whether disease activity is intermittent or continuous); and b) the situation of the psoriasis at the time of prescribing, that is, current disease activity (PASI), intensity of inflammation, and rate of deterioration (instability).
3. The patient’s preferences regarding the dosage regimen and the efficacy and safety profile of the drug.

**Final Note**

The prescribing physician should carefully read the instructions in the EMEA Summary of Product Characteristics and compare them with the recommendations in this consensus statement, particularly with regard to dose, contraindications, and possible interactions.

**Conflict of Interest**

L. Puig, X. Bordas, J.M. Carrascosa, E. Daudén, C. Ferrándiz, J.M. Hernanz, J.L. López Estebananz, J.C. Moreno, J.L. Sánchez Carazo, F. Vanaclocha, and H. Vázquez Veiga have received sponsorship from Abbott, MerckSerono, Novartis, Schering-Plough, and Wyeth for participation in clinical trials, and to attend or speak at meetings.

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Addendum

On February 19, 2009, while the present manuscript was in press, the European Medicines Agency (EMEA) recommended the suspension of the marketing authorization for Raptiva because of safety concerns including the risk of progressive multifocal leukoencephalopathy in patients receiving this drug.

The First Article in The Journal Actas Dermo-Sifiliográficas
Published With Photographs: Malignant Keratosis Diffusa Fetalis (Fetal Ichthyosis; Congenital Maligna Keratoma, Etc.),
by Juan de Azúa

Actas Dermosifiliográficas. 1909;1:77-90.

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Abstract. Brief comment is made on the first article published in the journal Actas Dermo-Sifiliográficas with photographic documentation of the case history and histological findings. It was written by the founder of the journal, Dr. Juan de Azúa, in 1909.

Key words: Actas, Azúa, photography, history

The first Actas Dermo-Sifiliográficas article in which photographs appear was the piece published by Azúa in 1909 entitled “Generalized malignant congenital hyperkeratosis (fetal ichthyosis; malignant congenital keratoma, etc.).”

Azúa describes a case "of a morbid, little known, and infrequent type that has been named in a variety of ways."

Subsequently, he stresses his interest in this patient, since “because severe cases usually result in death after the first hours or days of life, they are observed mainly by midwives, and it is rare for a dermatologist to be able to study them.”

Azúa was called in by a famous obstetrician at the Madrid maternity hospital, Dr Enrique de Isla, in May 1909, to “examine a child with a serious skin disorder, born that same day and not likely to survive long.” The patient, in fact, died that same afternoon, 10 hours after birth and a half hour before Azúa arrived at the maternity hospital.

Dr. Azúa takes note of the basic information: the mother was young and strong, not suffering from syphilis, and without skin disorders. The pregnancy and delivery were normal. The fetus was female, of average length and weight, born with respiratory distress and weak sucking reflex.

His description of his examination of the deceased infant is worth transcribing word for word: “The body was still warm. On it I observed, mainly in the folds of the joints, genital organs, neck, scalp, and ears a sebaceous coating, not very thick and dirty white in color, consisting of dead epidermal cells and fat, as subsequently confirmed. The entire skin surface was hard and stiff, resistant, inflexible: the horny layer resembled leather split in several places by long, deep, bloody cracks. These cracks formed radial patterns around the anus, vulva and mouth that recalled the fissures typical in cases of hereditary syphilis. The ears, with rudimentary and malformed auricles barely separate from the head, had a narrow auditory canal clogged with epidermal detritus. The extremely blunt nose had very small nostrils. The mouth was circular, and between its cracked, stiff, and immobile lips a fairly well-formed tongue appeared. The eyes were obscured by eyelid ectropion and could not be seen. Herniated conjunctivae appearing between the everted eyelids formed red protuberances… The vulva was open and flat, with small fissures around the vaginal orifice. There was not the slightest trace of hair, eyelashes or eyebrows.

On the hands and feet, the fingers and toes were cylindrical in shape and thin, the nail plate covered in a horny casing that obscured the nails…” (Figure 1). Figure

Figure 1. Case history