Diffuse normolipemic plane xanthoma (DNPX), a rare form of non-Langerhans cell histiocytosis, presents with xanthomatous skin lesions that develop independent of the serum lipid levels. It is commonly associated with hematologic diseases, which are usually diagnosed during the follow-up period.\(^1\) Data regarding DNPX is generally limited to single case reports, except for two case series which included 11 (part of a compilation of 63 cases with different diagnoses) and 8 study participants.\(^2,3\) Thus, in this case series of seven patients with DNPX, we aimed to evaluate the clinical and histopathological features of xanthomatous lesions, associated skin conditions, and accompanying hematologic diseases. We observed some novel clinical features of DNPX that have not been previously described. Furthermore, we screened the clinical photographs of approximately 70 articles from the PubMed database, focusing on the various clinical appearances of this rare disease.

Patients diagnosed with DNPX in our tertiary dermatology and venereology department between 2006 and 2023 were included in the study. The patient’s demographical, clinical, and histopathological findings as well as associated systemic diseases were retrospectively evaluated. This study was approved by the local ethics board (no: 2023/1326). Written and oral informed consents were obtained from the participants.

Our case series consisted of seven patients (six females and one male). The mean age of the patients was 53.4 ± 7.2 years (range, 47-67). The serum lipid levels of all the study patients were within the normal range. Morphological evaluation revealed large, yellow or orangish, flat plaques in all seven patients (Figure 1). Furthermore, in one patient, multiple dome-shaped yellow papular lesions were also on the elbow, and in another patient, three orangish nodular lesions were observed on the knee and elbow (Figure 2a). Histopathological examination of the biopsied plaque specimens from all patients revealed a subtle xanthomatous histiocytic infiltration in the dermis, which supported the diagnosis of DNPX. Histopathological examination of the nodule revealed an infiltration of numerous histiocytes with foamy cytoplasm and numerous multinucleated cells. This infiltration encompassed the entire dermis and was dispersed between the hypereosinophilic collagen bundles.

The face was involved in all the patients, and bilateral involvement of the periorbital region was predominantly observed (Figure 1a). In one patient, the periorbital plaque extended to the cheek (Figure 1b). The neck was the second most commonly involved site (n = 5) (Figure 1c, e; 2b). The plaques were also observed in the following areas: upper trunk (n = 4; Figure 1c, e), arms (n = 3), legs (n = 2), abdomen (n = 2), flexural areas (axilla and abdominal fold, and popliteal and antecubital regions; n = 2; Figure 1d, 2c), and back (n = 1). The skin folds of the neck were preserved in one plaque lesion (Figure 2b). In one of the patients with extensive axillary involvement, the axillary fossa was spared (Figure 2c). Similarly, a linear traumatic scar within a xanthomatous plaque was not involved (Figure 2b). In two patients, a halo of intact skin was observed around 11 senile angiomas within large xanthomatous plaques (Figure 2d, e). However, there was no halo of intact skin around one senil angioma within a plaque. In one patient, the abdomen and arms were involved, particularly the sites of striae (Figure 2f).\(^1\)

The following hematologic disorders were seen in the study patients: monoclonal gammopathy of undetermined significance (MGUS; n = 2), chronic lymphocytic leukemia (CLL; n = 1), chronic myelomonocytic leukemia (CMML; n = 1), acute myelogenous leukemia (AML; n = 1), and unexplained persistent monocytosis (n = 2). The patients with unexplained persistent monocytosis were evaluated for suspected
FIG. 1. a) Diffuse, yellow, flat plaques located bilaterally in the periorbital region. b) Yellow plaque seen extending from the periorbital region to the cheek. c) Well-demarcated, diffuse, yellow-orange, large, flat plaque on the chest and neck. d) Diffuse, yellow-orange, flat plaque in the axilla. e) Diffuse, yellow, flat plaque in the neck with tiny overlying papules.

FIG. 2. a) 1 cm-sized dome-shaped, orangish nodule on the elbow. b) Yellow-orange flat plaque on the chin and neck demonstrating sparing of skin folds and an old linear atrophic scar. c) Large, yellow-orange, flat plaque in the axilla without involvement of the axillary fossa (hair region). d) Patchy, yellowish, flat plaque on the chest demonstrating a halo of normal skin around two cherry angiomas. e) Halo sign around a cherry angioma within a patchy yellow plaque on back. f) Yellowish linear plaques involving multiple striae on the abdominal wall.
hematologic malignancy. The skin lesions appeared following the hematologic diagnosis (after 1, 1, and 4 years) in three patients. However, in two patients the DN PX lesions were present before the diagnosis of the systemic disease (5 and 8 years prior). Both patients with persistent monocytosis exhibited xanthomatous skin lesions for a much longer period (14 and 19 years) before the hematologic abnormality was detected.

Since the description of DN PX in 1962, only 95 cases have been reported. The disease is reportedly slightly more common in men than women and usually occurs in the 6th or 7th decade of life. The lesions are commonly located on the face (periorbital region), neck, and trunk.1,2,4 In our case series of seven patients, the average age of onset and commonly involved areas were similar to those in literature. However, more females than males were affected. DN PX is typically characterized by flat plaques of different size, which were present in all our patients. However, we also observed dome-shaped papules and nodules in two patients. The presence of papular and nodular lesions in addition to plaques has rarely been reported in the literature.1 In contrast to plaques, the nodular lesion in our study exhibited a dense histiocytic infiltration of the entire dermis with abundant multinuclear cells. This histopathological picture resembled that of a xanthogranuloma. Therefore, other clinical and histopathological features of both patients with papulonodular lesions were typical for DN PX, an association with adult xanthogranuloma could not be excluded.

We observed some novel dermatological findings in our patients, such as uninvolved areas within xanthomatous plaques or specific predilection of plaques for different pre-existing lesions. Although some of these findings have been highlighted in the literature, others have not received much attention (Table 1). Plaques usually demonstrate a diffuse pattern, with the sparing of some areas. In our case series, the axillary fossa, skin folds, scar site, and a halo around some senile angiomas were spared within some plaques. Sparing of the axillary fossa was first noted in 1970 by Bamba et al.5 who reported that lesions could involve the axilla but never affect the axillary fossa. Our review of several images from the relevant literature revealed a similar sparing within DN PX plaques in various regions, including the axillary fossa and pubic area.6-10 This finding has not been highlighted by all authors. However, diffuse axillary involvement including axillary fossa area was observed in one of our patients. Thus, axillary fossa sparing cannot be considered a rule of thumb. In one of our patients, we observed sparing of the neck skin folds. However, we did not identify a similar finding in any clinical images from the literature. The screening of previous DN PX clinical images also revealed areola sparing in one breast plaque.11 However, because no patient in our study exhibited a breast plaque, this finding could not be evaluated.

The presence of a halo of normal skin around senile angiomas within DN PX plaques was first noticed by Yu et al.2 in 1980. However, it was not reported for a long time. Since then, this finding has been mentioned in only some new case reports.7,12 We also observed a similar halo phenomenon in the clinical images of other reports in which the authors did not draw attention to this finding.13,14 In our study, this phenomenon was observed around 11 senile angiomas within xanthomatous plaques in two patients.

There was a marked predilection for certain areas, as opposed to areas spared, both in our patients and in the literature. Involvement of the striae (on the abdomen and arm) was observed in one of our patients, which has also been previously reported.3 In the initial years after DN PX was first described, Lynch and Winkelmann15 reported scar involvement in some patients. However, there have been no similar reports of scar involvement since then. In contrast, we observed sparing of the scar site in one xanthomatous plaque.

The etiopathogenesis of DN PX remains unclear. It has been suggested that phagocytosis of lipoprotein-paraprotein immune complexes by macrophages leads to cholesterol accumulation and formation of yellow plaques. Hida et al.12 reported that the blood flow in the spared halo around senile angiomas is decreased, which may be associated with the decrease in lipid accumulation. This mechanism may also explain the sparing of folds and scars. However, it cannot explain the sparing of the axillary fossa and areola. Thus, more data on the pathogenesis and clinical features of DN PX are required to explain all the specific involvement and sparing patterns.

### TABLE 1. Areas that are Predisposed to or Spared in Diffuse Normolipemic Plane Xanthoma Plaque Formation.

<table>
<thead>
<tr>
<th>Areas predisposed to lesion appearance</th>
<th>Areas spared</th>
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<tr>
<td>Classical morphology</td>
<td></td>
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<tr>
<td>Face (especially periorbital region)</td>
<td>Mucous membranes¹</td>
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<td>Neck</td>
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<tr>
<td>Upper trunk</td>
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<tr>
<td>Flexural areas (armpit, inguinal region, antecubital fossa, and popliteal fossa)</td>
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<tr>
<td>Novel dermatological findings</td>
<td></td>
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<tr>
<td>Areas of old scars¹</td>
<td>Areas of old scars*</td>
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<tr>
<td>Striae*</td>
<td>Axillary fossa* and genital region (hairy area)*</td>
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<td></td>
<td>Around cherry angiomas within a plaque*⁵,7,12-14</td>
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<td></td>
<td>Around areola¹¹</td>
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<td>Skin folds*</td>
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*Finding in our patients.
DNPX is reportedly associated with hematologic malignancies, particularly MGUS and multiple myeloma. In our case series, hematologic abnormalities were detected in all patients. The most common abnormalities were MGUS and leukemia (CLL, AML, and CMML). The hematologic disease was diagnosed before and after the emergence of skin lesions in three and four patients, respectively. In the two patients with persistent monocytosis, the skin lesions had appeared long before the diagnosis of the hematological abnormality (14 and 19 years). Similarly, in the literature, the hematologic condition was diagnosed in some patients long after the appearance of their skin lesions, with the longest interval being 15 years. As hematologic abnormalities may develop long after the appearance of skin lesions all patients require close follow-up.

In conclusion, plaques seen in DNPX may demonstrate specific involvement patterns, with sparing of some anatomic areas such as axillary fossa, pubic area, areola, skin creases, and scars. Furthermore, the plaques may demonstrate a predilection for some scars and striae. An uninvolved halo around senile angiomas within xanthomatous plaques may be considered a unique finding of this disease. Furthermore, there is a strong association between DNPX and hematologic diseases, which may be diagnosed before or long after the appearance of DNPX skin lesions.

REFERENCES