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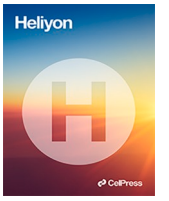

Case report

Erythema nodosum as first clinical manifestation of metastatic neuroendocrine tumor: A case report☆

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ABSTRACT

Erythema nodosum (EN) is a reactive inflammatory panniculitis, which has been associated with medications, infections, autoimmune and autoinflammatory diseases. It has rarely been associated with neoplasms. We present the case of a 61-year old woman who was admitted because 3-week history of painful erythematous subcutaneous nodules on the lower limbs clinically consistent with EN, which was confirmed by skin biopsy. The patient denied use of medication. No general or systemic symptoms were present. As part of his study, an abdominal ultrasound and later magnetic resonance imaging (MRI) was done and lesions suggestive of liver metastases were reported. An ultrasound guided liver biopsy was then performed and pathology studies evidence a well differentiated grade II gastro-enteropancreatic neuroendocrine tumor (GEP-NET). A 9mTc-Octreotide scintigraphy evidenced a positive expression of somatostatin receptor in the liver and in a nodular mesenteric lesion in contact with an intestinal loop.

The patient began treatment with lanreotide and was scheduled for cytoreductive surgery. During surgery, 50 cm of the small intestine, gallbladder, mesenteric fat and a 4.2x3.3 × 1 cm tumor located on the VII hepatic lobe were resected. Subsequently EN lesions of the lower extremities resolved.

We present a rare case of GEP-NET-associated EN, that improved with surgical tumor cytoreduction and hormone therapy.

1. Introduction

Erythema nodosum (EN) is a reactive inflammatory panniculitis characterized by erythematous subcutaneous nodules located mainly in the lower limbs [1]. First described by Robert Willian in 1798 [2], EN shows characteristic feature of septal panniculitis without vasculitis [3]. Its incidence usually varies according to triggering factors and it has been reported to be as low as 54 cases per million [4]. As much as 32–72 % of EN cases will remain of unknown etiology, being infectious diseases (beta-hemolytic *Streptococcus*,

☆ Data included in article is referenced in the article.

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Staphylococcus aureus, *Mycobacterium tuberculosis,* among others), systemic diseases (as sarcoidosis, inflammatory bowel disease, Behçet's disease, systemic lupus erythematosus, systemic vasculitis, among others) and drugs (antibiotics, oral contraceptive, angiotensin-converting enzyme inhibitors, or proton pump inhibitors), the most common triggers [3]. Although neoplasia is less frequently found to be the underlying cause, hematologic malignancies (Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia) are most frequently associated with EN [1,3]. Rarer are the cases reported with solid tumors including carcinoid tumor [5–9]. We report a case of paraneoplastic EN associated with metastatic gastro-enteropancreatic neuroendocrine tumor (GEP-NET) of the small intestine with multiple liver metastases. The treatment indicated to achieve tumor reduction were associated with remission of EN.

1.1. Case report

Informed consent for publication was obtained from the patient. The patient was evaluated and treated at Fundación Valle del Lili, a high-complexity hospital in Cali, Colombia.

A 61- year old woman presented to the rheumatology department with a 3-week history of painful erythematous subcutaneous nodules on the lower limbs. The patient had no history of chronic or recent acute disease and was considered healthy prior to these symptoms. She denied use of medication. Physical examination revealed multiple erythematous palpable nodules of the lower limbs (Fig. 1A).

Initial diagnostic tests were performed showing mild increase of both C-reactive protein and erythrocyte sedimentation rate (2.22 mg/dL and 30 mm/h respectively). Total blood count, renal function tests, liver tests and bone mineral metabolism tests were normal (Table 1). Skin biopsy of a nodular lesion was performed and it confirmed septal panniculitis without vasculitis, findings compatible with erythema nodosum (EN) (Fig. 1B).

An abdominal ultrasound as part of the initial study revealed nodular lesions in the liver, which were best characterized by abdominal Magnetic Resonance Imaging (MRI) that reported multiple metastatic hyperintense lesions of the liver. Further analysis, such as angiotensin converting enzyme levels and tumor markers were found to be normal (Table 1).

The patient was scheduled to do a full body fluorine-18 fluorodeoxyglucose positron emission tomography that revealed hypermetabolic masses on the VIII-IVB segments of the liver with high suspicious infiltrative state.

An ultrasound guided liver biopsy was then performed with evidence of a well differentiated grade II gastro-enteropancreatic neuroendocrine tumor (GEP-NET) (Neoplastic cells showing positivity for CKAE1-AE3, chromogranin, synaptophysin and CDX2; being negative for CD56, TTF-1, CK7, and ARGINASE). The cell proliferation index given by KI-67 was 8.

A 9mTc-Octreotide scintigraphy was then performed with evidence of positive expression of somatostatin receptor in the liver and in a nodular mesenteric lesion in contact with an adjacent intestinal loop (Fig. 2).

Serum levels of chromogranin A were reported at 243 ng/mL (N:19,4–98,1 ng/mL) and a 24-h urine 5 - hidroxi-indoleacetic acid level of 29.2mg/24h (N: 2–9 mg).

The patient began treatment with lanreotide and was scheduled for cytoreductive surgery. During surgery, 50 cm of the small intestine, gallbladder, mesenteric fat and a 4.2x3.3 × 1 cm tumor located on the VII hepatic lobe were resected. Further pathological findings revealed a solid, submucosal mass of 0.7x0.7 × 0.4 cms on the small intestine and the presence of a 2.7x1.4 × 1.3 cms. mass immersed on the mesenteric fat. Tumor cells of the small intestine were positive for CKAE1/AE3, Sinaptophysin, Chromogranin, CD56 and CDX2 with a Ki-67 proliferation index <1 % confirming the diagnosis of GEP-NET. The metastatic hepatic tumor had a Ki-67 proliferation index <1 % (Fig. 3A–F).

At follow-up one and six months after the surgery the patient remained asymptomatic and is receiving lanreotide with good tolerance. EN lesions of the lower extremities resolved.

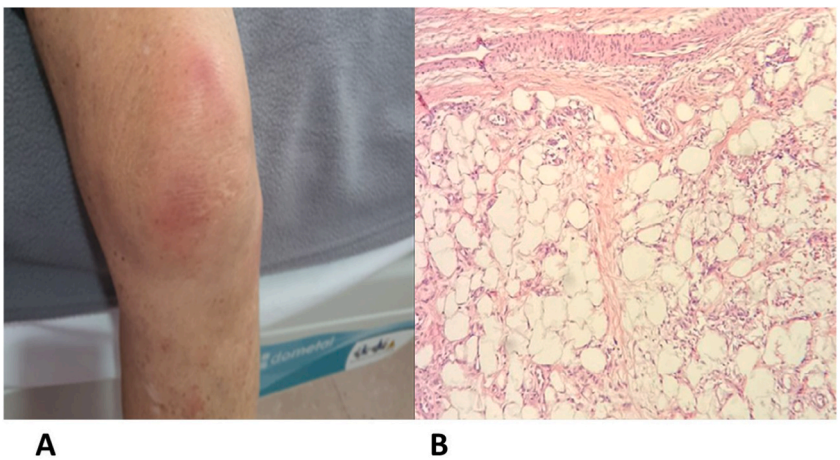

Fig. 1. A: Multiple erythematous palpable nodules of the lower extremities. B: Hematoxylin and eosin stain showing septal panniculitis without vasculitis, compatible with erythema nodosum.

Table 1
Most relevant laboratory values.

Examan	Result	Normal value
Hemoglobin (g/dL)	13,3	12–16
Hematocrit(%)	39,7	34,1–44,9
Leukocytes(x10^3/μL)	7,53	3,98–10,04
Neutrophils (x10^3/μL)	5,14	1,56–6,13
Limphocytes (x10^3/μL)	1,44	1,18–3,74
Plaquete count (x10^3/μL)	399	150–450
Erythrocyte Sedimention Rate (mm/h)	**30**	0–20
Serum creatinine (mg/dL)	0,81	0,51–0,95
Ureic nitrogen (mg/dL)	13,4	2–20
Alaline Transaminase (U/L)	17,6	0–31
Aspartate Aminotransferase (U/L)	19,9	0–32
Total calcium (mg/dL)	10,19	8,8–10,20
Phosphorus (mg/dL)	3,39	2,5–4,5
Intact Parathohormone (pg/ml)	45,3	15–65
C- reactive protein (mg/dL)	**2,22**	0-0,5
Angiotensine converter enzime (U/L)	27,5	9–67
CEA (ng/mL)	1,14	0-3,0
CA-125 (U/mL)	10,3	0–35
CA-19,9 (U/mL)	5,9	0–39
Alphaphetoprotein (ng/mL)	2,99	0-8,7

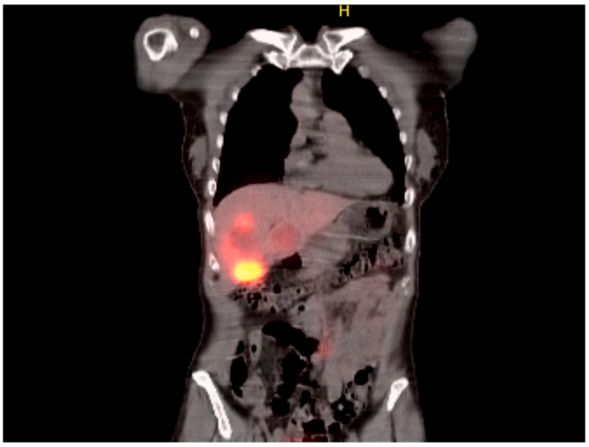

Fig. 2. 9mTc-Octreotide scintigraphy shows positive expression of somatostatin receptor in the liver and in a intestinal loop.

2. Discussion

GEP-NETs are relatively uncommon heterogeneous neoplasms arising from endocrine and neuronal origin cells showing highly variable clinical behavior. Studies have shown that up to 14 % of patients with histologically proven GEP-NETs at the time of diagnosis already have metastasis (most commonly of the liver) [10]. Well-differentiated GEP-NETs can be classified as low grade (Ki67 % index <3 or Mitotic rate per 2 mm2 of 0–1), intermediate grade (Ki67 % index 3–20 or mitotic rate per 2 mm2 of 2–20) or high grade (Ki67 % index >20 or Mitotic rate per 2 mm2 of >20) [11,12]. Our patient had a low grade GEP-NET.

In general, GEP-NETs incidence has been increasing very probably due to improvement of diagnostic techniques. GEP-NETs generally do not cause carcinoid syndrome; our patient had elevated urinary 5-hidroxi-indoleacetic acid without carcinoid syndrome symptoms. These findings are more commonly associated with GET-NETs of duodenal (gastrinoma or somatostatinoma) origin and jejunal/ileal GET-NETs that metastasize to the liver [12], like our patient.

Similar to our case, Lin JT et al. in 2004 reported the first association of a carcinoid tumor located in the retroperitoneum with concomitant EN [13]. This case is about a 45-year-old man with EN on the lower extremities of 4 months' duration, and lost 20 kg in weight. He complained of concomitant vague bilateral flank pain. CT scan of the abdomen showed a 20-cm retroperitoneal heterogenous mass and histopathological examination revealed infiltrating nests of carcinoma cells with rosette formation and immunohistological analysis revealed positivity for neuroendocrine markers (synaptophysin and chromogranin). Urinary 5-hidroxi-indoleacetic acid was normal (unlike our case, which was elevated). Carcinoid syndrome was not present. The patient received chemotherapy with four cycles of cisplatin and etoposide. EN disappeared shortly after the first cycle. This case and ours are similar in terms of response to treatment. In both cases EN remitted with treatment of the neoplasia.

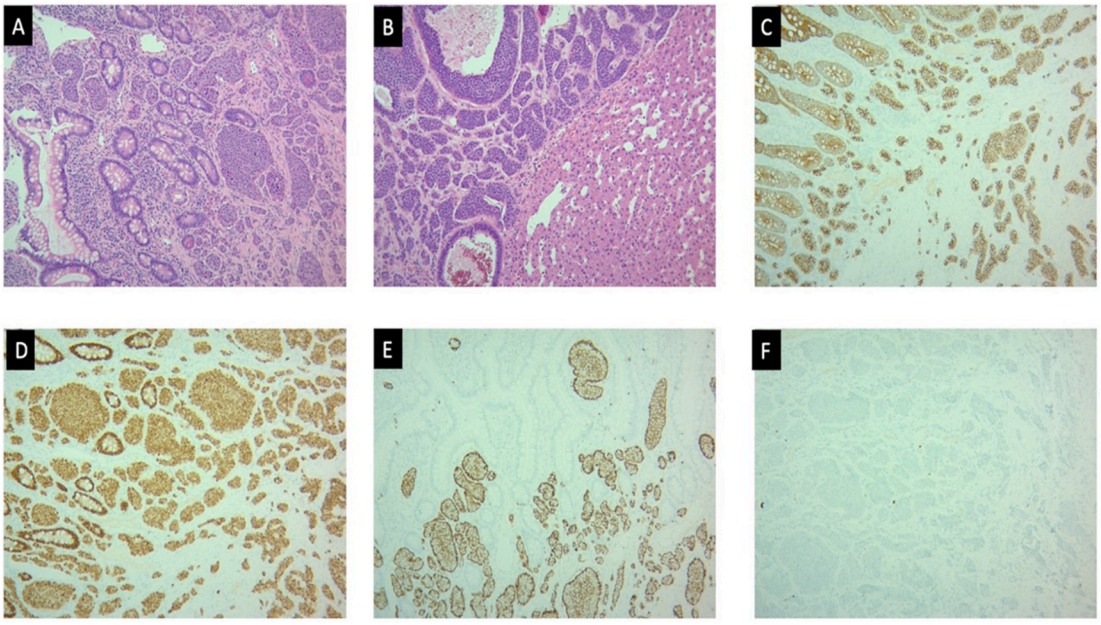

Fig. 3. Histopathological and histochemical characteristics of the tumor. A- Hematoxylin and eosin stain of tumor of the small intestine (10x). B- Hematoxylin and eosin stain of metastatic tumor on the liver (10x). C - Citokeratin AE1/AE3 (10x) D- CDX2 (10x). E– Chromogranin (10x). F- Ki67 (10 x).

Malignancy and EN has been rarely described with solid tumors including lung cancer [5], adenocarcinoma of colon [6], carcinoma of the uterine cervix [7], and hepatocellular carcinoma [8]. The EN runs a parallel course with the cancer, similar to the findings in our case with the disappearance of skin manifestation with treatment of the neoplasia.

The underlying mechanism of these cases is unclear but has been postulated that it may be due to deposition of immune complexes [13,14]. An immune dysregulation was been proposed as pathogenic role in paraneoplastic syndromes associated with carcinoid tumors [15].

We report a case of EN associated with low grade GET-NET of the small intestine with multiple liver metastasis in which after appropriate tumor treatment, EN resolved. We present a rare cause of EN that must be taken into account when facing a patient without apparent cause of EN.

CRediT authorship contribution statement

Daniel Barona-Rommy: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Juan C. Bravo:** Writing – original draft, Conceptualization. **María J. Varela:** Writing – original draft, Methodology, Conceptualization. **Luis G. Arango:** Writing – original draft, Methodology, Conceptualization. **Carlos A. Cañas:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization.

Ethics statement

The author declares no conflict of interest.

Written informed consent for publication was signed by the patient.

Declaration of competing interest

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

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