

# Epidermodysplasia Verruciformis Associated with Astrocytoma, Mantle Lymphoma and Hepatitis B Virus Infection

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**Abstract** Epidermodysplasia verruciformis (EV) is a lifelong, rare autosomal recessive genetic hereditary skin disorder characterized by a unique susceptibility to human papilloma virus, associated with a high risk of malignant transformation. The disseminated verrucous lesions and pityriasis versicolor-like lesions persist from early childhood and can transform into a cutaneous malignancy in a fourth of patients. No definitive treatment against Epidermodysplasia verruciformis has been found yet. Extracutaneous cancers reported in Epidermodysplasia verruciformis are intestinal adenocarcinoma, plasmablastic lymphoma and leiomyosarcoma. Mantle cell lymphoma is uncommon under the age of 40 years and rare in patients under the age of 30 years. Here we are reporting a 19 year male patient with Epidermodysplasia verruciformis, astrocytoma and pulmonary tuberculosis who presented with symptoms of weight loss, indigestion and burning epigastric pain four months duration, Upper GIT endoscopy showed a gastric mass with active peptic ulcers. Biopsy revealed Mantle cell lymphoma. We investigated further and found to have immunodeficiency and hepatitis B virus infection. EV patients should receive regular follow-up for possible cutaneous or extracutaneous malignancy.

**Keywords:** *Epidermodysplasia verruciformis, Astrocytoma, Lymphoma, Mantle-Cell, Human papillomavirus DNA Tests, Hepatitis B virus*

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## 1. Background

Lewandowsky and Lutz dysplasia which also called as Epidermodysplasia verruciformis (EV) is an extremely rare autosomal recessive genetic hereditary skin disorder associated with a high risk of malignant transformation [1]. It has no racial or geographic predilection, but increased incidence in consanguineous marriages [2]. It is characterized by abnormal susceptibility to human papilloma viruses (HPVs) of the skin [3]. The resulting uncontrolled HPV infections result in the growth of scaly macules and papules, particularly on the hands and feet. It is typically associated with HPV types 5 and 8 which are found in about 80 percent of the normal population as asymptomatic infections [4,5]. The condition usually has an onset between the ages of 1–20, but can occasionally present in middle-age without gender predisposition [6]. It is named after the physicians who first documented it, Felix Lewandowsky and Wilhelm Lutz [7].

Carcinogenic cofactors, such as ultraviolet ray irradiation, decreased the cell mediated immunity and impaired DNA repair are probably involved in the progression from benign warts (verrucae) to cancer [8,9,10,11].

Malignant transformation of skin lesions, particularly squamous cell carcinoma has been observed in more than half the patients followed for 20-30 years. Malignant tumors are typically found after age 30 years, usually during the fourth and fifth decades of life [12,13].

No definitive treatment for EV has been found yet. Treatment of EV includes preventive measures, the most important of which are the strict sun protection and life-long observation for early diagnosis of malignant/premalignant lesions for improved survival. Acitretin (0.5-1 mg/ day) is the effective and the palliative drug of choice [14].

We report this young patient who had Astrocytoma, pulmonary tuberculosis, Mantle cell lymphoma, Hepatitis B Virus infection and immunodeficiency after the previous diagnoses of EV represent an interesting uncommon occurrence of these diseases together.

## 2. Case Report

A 19-year-old orphan boy, born to second-degree consanguineous parents, he had been well until 6 years of age when his mother found multiple asymptomatic dark colored and light colored lesions over the neck and trunk. At the age of 8 years, a prominent, persistent dark raised

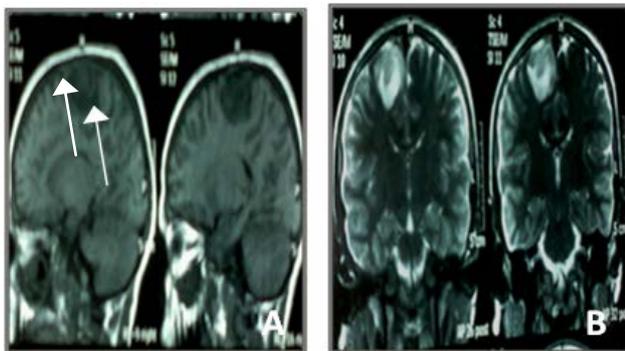
eruption appeared on both sides of the forehead and near the lateral canthus of the eyes. After skin biopsy and other laboratories testing work up, the patient was diagnosed as a case of Epidermodyplasia verruciformis. The patient had received some form of treatment (retinoid) for 10 months, but without any improvement. None of his living family members (total 13) had this disease. At the age of 9 years, he began to show delayed growth and received hormonal therapy without improvement.

The patient was admitted to Sohag University Hospital in September 2012 for evaluation of history of left focal seizures associated with left focal neurological deficits where computer tomography was done and showed a well defined right parietal hypodense lesion. The laboratory testing revealed negative or normal values for collagen disease, vasculitis and hypercoagulable state [ANA test, anti-DNA antibodies, rheumatoid factor, lupus anticoagulant, ANCA (cytoplasmic and perinuclear), anti-SS-A antibodies, anti-RNP antibodies, anticardiolipin antibodies and Protein C and S] which were considered a possible candidate for his condition.

Echocardiography and MRV of the brain was normal, but brain Magnetic resonance imaging (MRI) revealed a well defined right high parietal wedge shaped cortical lesion with low T1W and high T2W signal intensities measuring  $2.5 \times 2 \times 2.3$  cm [Figure 1], when Astrocytoma was diagnosed after that radiotherapy (ten cycles) was administered for the lesion (Details not available). The patient discontinued the treatment after improvement in the neurological deficit and stopping the seizure.

One year ago, the patient developed a productive cough of yellowish sputum and at that moment, was diagnosed as a case of smear positive pulmonary tuberculosis and anti-tuberculous agents were administered for 6 months. Screening was done after the end of treatment and 3 months later by chest imaging and sputum smears which revealed negative results.

The patient was admitted to Sohag University Hospital again in February 2014 because of history of generalized fatigue, unexplained weight loss, indigestion, epigastric fullness, burning epigastric pain related to the meal which improved on vomiting and proton pump inhibitors. No history of fever, recurrent focal neurological deficit, seizures or body swellings.



**Figure 1.** MRI brain (A) T1W and (A) T2W showing right high parietal wedge shaped cortical based lesion

Vital signs were stable and physical exam was unremarkable except for his body weight was 32 kg, height of 137 cm (BMI =17.05), with multiple mildly erythematous, scaly, hypopigmented, pityriasis versicolor-like lesions were present over the trunk and extremities

and multiple brownish-black hyperkeratotic verrucous papules and plaques were present over the extremities, neck, and face [Figure 2].



**Figure 2.** Clinical Photographs of the Patient: Multiple pityriasis versicolor-like lesions with few brownish-black hyperkeratotic verrucous papules and plaques present over the (A) face, (B) back, and (C) forearm

He had not initiated male external genitalia development with absent secondary sexual characteristics with normal pre-pubertal male external genitalia which indicating delayed puberty associated with growth failure. At that moment, laboratory tests revealed normal blood sugar, urine analysis and serum biochemistry except hypoalbuminemia. There were no abnormalities in hemoglobin level, platelets and RBCs count. The total white blood cells (WBCs) fell within the normal range.

However, our patient had lower frequencies of lymphocytes (1068 counts/ $\mu$ l) (normal range = 1120–3370). Flow cytometric immunophenotyping analysis of peripheral blood of the patient showed decreases in total numbers of T lymphocytes, T-helper cells (CD4+T) and T suppressor cells (CD8+ T).

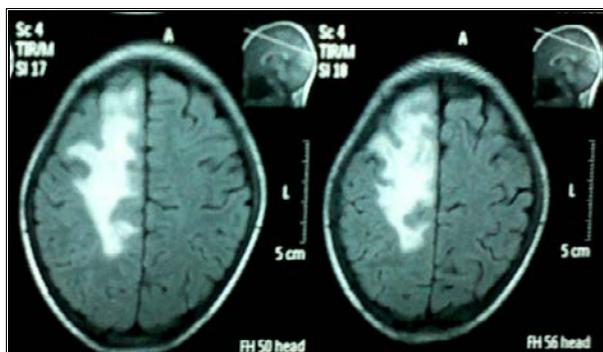
Flowcytometric analysis of peripheral blood demonstrated 50% CD3+cells (normal range = 64–85), 16.5% CD4+cells (normal range = 34–62), 9.45% CD8+cells (normal range = 14–42) with a CD4+/CD8+cell ratio of 1.74 (normal range = 0.9-3.52) and 0.25% CD19+cells, 0.5% CD23+cells, 0.5%CD22+cells, 0.5%CD79b+cells with low expression of all immunoglobulin heavy chains IgA, IgG, IgM, IgD. Our patient had a significant decrease in surface immunoglobulin. Serum C3 and C4 levels were within normal limits.

He had normal C-reactive protein, lipid and hormonal profiles except low serum testosterone level. A summary of the laboratory tests are shown in Table 1.

**Table 1. Laboratory test results**

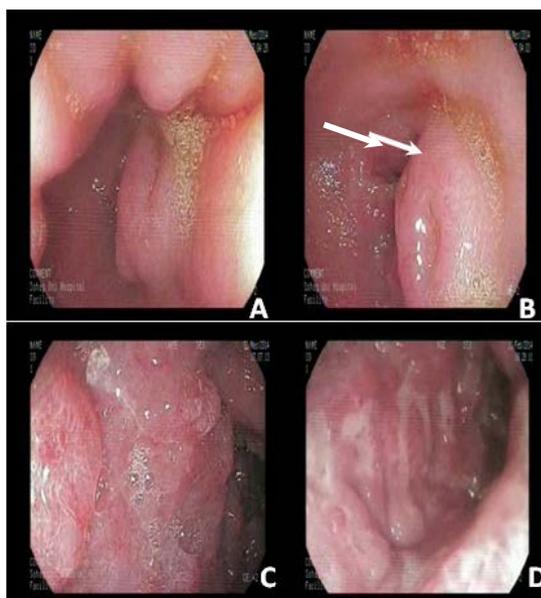
| Test     | Patient results        | Normal values                                 |
|----------|------------------------|---|
| WBC      | 8.900/mm <sup>3</sup>  | 4.0 – 10.0 X 10 <sup>3</sup> /mm <sup>3</sup> |
| RBCs     | 6.31M/uL               | 4.4 – 5.7 X 10 <sup>6</sup> /mm <sup>3</sup>  |
| Hb       | 13.2/dL                | 12.0–16.0 g/dL                                |
| PLT      | 392 K/uL               | 150–450 K /uL                                 |
| UA       | 3.7mg/dl               | 3.4-7   |
| LDH      | 383 U/L                | 141– 247 U/L                                  |
| Free T4  | 1.05 ng/mL             | 0.89-1.76                                     |
| Free T3  | 4.04pg/mL              | 1.50-4.10                                     |
| TSH      | 1.89 uIU/ml            | 0.40-4.00                                     |
| FSH      | 4.38mIU/ml             | 0.7-11.1                                      |
| PRL      | 5.02ng/mL              | 2.5-17.0                                      |
| TES      | <20.0ng/dL             | 262-1593                                      |
| E2       | 24.4pg/mL              | 0.00-56                                       |
| Growth H | 1 <sup>st</sup> sample | 3.09 ng/mL                                    |
|          | 2 <sup>nd</sup> sample | 4.35ng/mL                                     |
| ESR      | 1 <sup>st</sup> h      | 8   |
|          | 2 <sup>nd</sup> h      | 24  |

Abdominal U/S was normal except dilated intestines. The patient underwent, another CT and MRI brain to screen old lesion which showed well defined right high parietal cortical based lesion larger than the old lesion, but nearly at the same site [Figure 3].



**Figure 3.** MRI brain an axial T2-weighted image shows right high parietal cortical mass

Upper GIT endoscopy showed scattered small sized active ulcers (stage A1) at antrum and pyloric ring of the stomach, which distorted with submucosal mass like lesion [Figure 4].

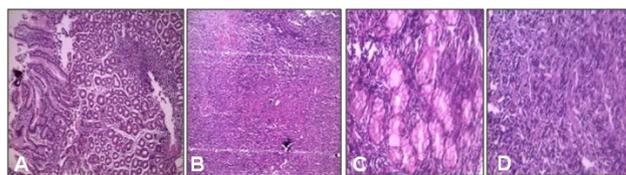


**Figure 4.** Upper GIT endoscopy showed: (A,B) Submucosal mass at pyloric ring of stomach. (C) Duodenum is edematous and erythematous. (D) Scattered small sized active ulcers at antrum, pyloric ring of stomach and duodenum

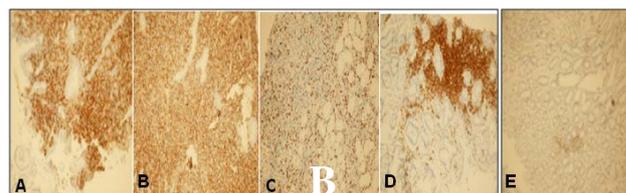
Pathology report of the endoscopic biopsies revealed an ulcerated malignant lymphoma [Figure 5].

On immunohistochemistry, these tumor cells were LCA, CD20, CD5 and Cyclin D1, positive and CD 3 negative. A final diagnosis of non Hodgkin lymphoma, mantle cell lymphoma was made [Figure 6]. The patient's bone marrow obtained by aspiration showed no evidence of lymphoma involvement.

Serological viral studies revealed negative results of HIV and hepatitis C virus antibodies, but hepatitis B surface antigen (HBs) was positive. The same investigation for his mother revealed negative results of HIV, hepatitis C virus antibodies and hepatitis B surface antigen (HBs). The father who died early after a motor car accident, did not have history suspected of HBV infection.

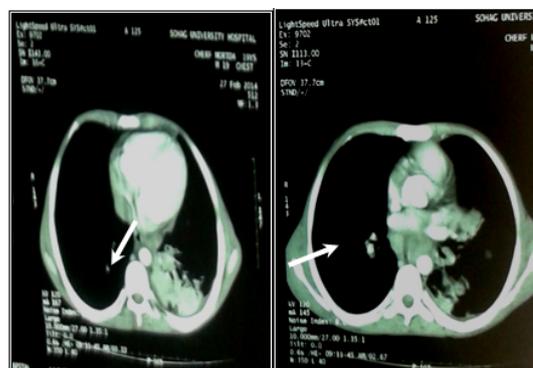


**Figure 5.** Pathological Examination of Biopsy Specimens from Stomach and duodenal showing (A, B) Low power view, H&E: Fragments of gastric mucosa with extensive ulceration, (C,D) high power view, H&E: showing dense diffuse infiltrate by neoplastic lymphoid cells large and intermediate with moderate vascularity

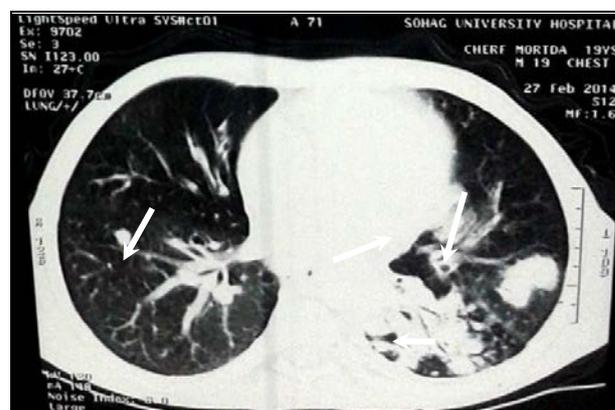


**Figure 6.** Immunophenotype of stomach and duodenal biopsies revealed tumor cells positive for (A) LCA, (B) low power and (C) high power: diffuse cells positive for CD20, (D) CD5 positivity and (E) Cyclin D1 positive

3 weeks later before starting chemotherapy, further examinations showed a generalized small lymphadenopathy with mild hepatosplenomegaly and abnormal liver function tests. A whole body computerized axial tomography (CT) scans showed mild hepatosplenomegaly, ascitis and a markedly aggregated, mesenteric, retroperitoneum, peripancreatic, portohepatic and mediastinal lymphadenopathy with multiple lung nodules [Figure 7, Figure 8].



**Figure 7.** Mediastinal windows- shows mediastinal adenopathy and mass like lesion seen at posterior segment of right middle lobe



**Figure 8.** Lung window - multiple lung nodules and discrete mass like lesion seen at posterior segment of right middle lobe with small thick walled cavity also note irregular inner rim

He was diagnosed as having a B cell lymphoma (mantle cell lymphoma), classified as stage IV according to the Ann Arbor classification modified by Musshoff et al. [15] and by the International Workshop in Lugano, Switzerland [16].

The patient underwent chemotherapy with CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone) regimen for his lymphoma. Seven weeks after two cycles of chemotherapy, the patient developed renal impairment, pancytopenia, generalized edema, marked respiratory distress and died.

### 3. Discussion

Epidermodysplasia verruciformis (EV) is a rare genodermatosis which may occur in either a classical form or in association with various hereditary or acquired immunodeficiencies [17]. EV is most commonly inherited in an autosomal recessive manner, although sporadic, sex-linked, and autosomal dominant inheritance has been described [18,19].

In classical EV, the cutaneous lesions start to appear early in childhood (61.5% in children aged 5-11 yr) like our case report. A subset of patients may present at puberty (22.5%) and lastly the disease manifests as a congenital form in infancy (approximately 7.5%) [6,20,21,22].

EV has been reported in various immunosuppressed states (sometimes referred to as "EV-like lesions") including HIV [23,24,25], graft versus host disease [26], renal transplantation [27], systemic lupus erythematosus [28], Hodgkin disease [29], WILD syndrome (warts, immunodeficiency, lymphedema, anogenital dysplasia) [30] which were excluded in our patient and also has been reported in common variable immunodeficiency [31,32] and also in isolated IgM deficiency [33,34].

The pathogenesis of EV may be explained by three factors: genetic factors, HPV infection and immunological factors. As our patient most EV patients have been found to have an impaired cell-mediated immunity [35]. Aoyama H, et al. reported association with EV and hereditary abnormal expansion of large granular lymphocytes and a decrease in T cells [36]. There are also case reports regarding the association with idiopathic CD4 lymphocytopenia and EV-like eruptions [37,38].

Majewski et al. reported that natural cell-mediated cytotoxicity was in the normal range in EV patients [39]. Recently, Stray-Pedersen et al. reveal the third CORO1A-mutated kindred, in Siblings with T-B+NK+ severe combined immunodeficiency (SCID) [40].

Our case had an impaired cell-mediated immunity and significant decrease in surface immunoglobulin with normal Serum C3 and C4 levels. However the type of immunodeficiency couldn't be identified because the changes that occur in the expression of immunoglobulin heavy chains (IgM and IgD, IgG and IgA) by the effect of the mantle B cells (MC) lymphoma as well as other investigations for diagnosis could not be done in our patient due to financial constraints.

There are also case reports regarding the association with leprosy and EV, one of them describe an EV patient with a localized form of *M. Leprae* infection, confirming that tuberculoid leprosy patients possess a relatively

specific and efficient cell-mediated immunity against the bacillus [41]. The converse situation occurred in two African sisters suffering from lepromatous leprosy who had EV [42].

In contrast, to tuberculosis, clinical leprosy does not appear more frequently in several types of immunodeficiency as our patient who suffered from pulmonary TB.

Zantour B et al. report the case of a female patient had EV, Familial idiopathic pulmonary fibrosis associated with autoimmune polyendocrinopathy, with the absence of pubertal development. Endocrine explorations detected hypogonadotropic hypogonadism, primary hypothyroidism and MRI revealed an empty sella turcica [43], our patient's hormonal profiles were normal except low serum testosterone level (hypogonadism).

There are two main clinical forms of EV have been identified, benign and malignant. In benign skin lesions, the viral cytopathic effect was only observed in the upper layers of the epithelium [44,45].

EV is accepted as a pre-malignant condition. Malignant changes may occur in the form of actinic keratosis, Bowen's disease, Squamous cell carcinoma, basal cell carcinoma, or rarely sweat apparatus carcinoma. Squamous cell carcinoma (in situ or invasive), develop frequently in these patients (30–70%), most commonly on sun-exposed areas starting between the ages of 20 and 40 years [46], but our patient did not develop malignant transformation of his skin lesions during follow-up. This could be explained by the age of our patient less than 20 years.

EV is associated with several types of human papillomavirus, but types 5, 8, and 47 are closely associated with malignant EV lesions which selectively retain and express the E6 and E7 portions of the viral genome. These viral proteins cause cell immortalization, or failure of apoptosis, resulting in transformation of normal human keratinocytes into malignant cells [47], [48].

A decrease in UV-induced DNA repair synthesis, coupled with an oncogenic viral infection may play an important role in somatic mutations and malignant transformation in patients with EV [6,49,50], but the precise pathogenesis of the onset of the internal malignancies are unknown.

Extracutaneous cancers reported in EV are intestinal adenocarcinoma [51], plasmablastic lymphoma [52], natural killer/T cell lymphoma [53] and intestinal lymphoma [54]. A similar instance of EV, disseminated molluscum contagiosum and intestinal diffuse large B cell lymphoma has been published [55]. Although Co morbidity of EV and lymphoma has previously been documented, the causes of this association are not clear.

There are several aspects of this association such as: The first one is whether EV-type HPVs may cause lymphomagenesis and have oncogenic properties by playing roles in cell immortalization, proapoptotic/antiapoptotic pathways, chromosomal destabilization, and activation of telomerase [56,57]. Moreover, the lymphomagenic effects of some HPV subtypes are described [58].

The second aspect is immunosuppressive background. Lymphomas occur in patients with impaired immunity. EV is also more frequent in immunosuppressive patients

[59,60]. And as previously mentioned, some abnormalities of nonspecific cell-mediated immunity have been found in patients with EV. These include decreased absolute numbers of T lymphocytes and T helper cells with a reversed CD4+/CD8+ ratio [39,61]. The association between lymphoma and EV are mostly due to immunosuppression, so we can hypothesize that T-cell deficiency may lead to unchecked B cell proliferation.

Other extracutaneous cancers reported in EV are leiomyosarcoma in a 6-year-old child with an immune defect and Myelodysplastic syndrome also has previously been documented [62,63].

Even with extensive search we found few data regarding the association between EV and astrocytoma, but the association between treated astrocytoma and the occurrence of non-Hodgkin's lymphoma were reported [64].

So we can, hypothesize that are there associations between EV and astrocytoma? Or treated astrocytoma may represent predisposing factors of the occurrence of lymphoma.

The present case reports an interesting, uncommon occurrence of astrocytoma, pulmonary TB, mantle cell lymphoma, Hepatitis B Virus infection with EV. Our research of the literature yielded no similar presentation of EV and these diseases.

There are no known risk factors associated with an elevated risk of developing MCL except aging. MCL is rare in patients under the age of 30 years. At the M.D. Anderson Cancer Center, the youngest patient with MCL to date was 24 years old. Our patient was diagnosed as a case of Mantle cell lymphoma under the age of 20 years. There is a case report of an 18-year-old girl with blastoid variant MCL.

Our patient had been incidentally affected by HBV infection. There is a report indicating concomitant presence of squamous cell carcinoma and HCC in a patient with EV and associated chronic HBV infection [65] and another case report describe the rare occurrence of plasmablastic lymphoma in a patient with long lasting EV and hepatitis B virus infection [52].

NO data are currently available regarding the relation between co-infection with HBV and development of secondary malignancies in EV patients. There are several aspects of this association such as: pre-existing multiple comorbidities (MCL, TB, Astrocytoma, radiotherapy, EV) may represent predisposing factors for HBV reactivation similar to other studies which reported that in immunocompetent people, EBV is never completely eradicated and a small number of EBV-infected B cells remain latent and capable of reactivation at a later time. Furthermore, the gene products of latently infected B cells may contribute to B-cell immortalization [66] or viral infection (HPV and HBV) with radiotherapy making them susceptible to genetic mutations.

## 4. Conclusion

We believe that the etiology and pathogenesis of extracutaneous cancers in EV patients still remain poorly understood and the findings of this case report will highlight the importance of early diagnosis and further observational studies would need to be carried out for clarification of the latter.

The concomitant HBV infection is usually discovered incidentally in EV patients, so we should search in relation between co-infection with (HPVs, HBV), immunodeficiency and the development of secondary malignancies in EV patients.

## 5. Consent

Written informed consent was obtained from the patient for publication of this case report and the accompanying figures.

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## Disclosure

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