Background: The Ectopic ACTH Syndromes (EAS) often associated with severe hypercortisolism (HC) are really a challenge.

Case presentation: We report the case of a 48-year-old woman with ectopic adrenocorticotropic hormone secretion (EAS) confirmed biochemically and by bilateral inferior petrosal sinus sampling. Not conclusive left-adrenal topography in all imaging studies was found, even somatostatin receptor scintigraphy (SSRS) and 123I-metaiodobenzylguanidine. Due to positive SSRS, medical treatment with high-dose extended-release somatostatin analogs (SSAs) was initiated but patient’s condition worsened dramatically one week later. Immediately after cortisol normalization with ketoconazole the patient underwent surgery. Her left adrenal gland and a contiguous lesion, that resulted to be, an associated extra-adrenal ganglioneuroma, were removed but surprisingly only the adrenal medulla had significant staining of adrenocorticotropic hormone (ACTH). After surgery, the patient improved, blood pressure normalized without medication, and her hypercortisolism and clinical symptoms were resolved.