ENEA 2022 Immunohistochemichal expression of ephrin receptor (EPH)-A4, -A5, -B2, -B5 and SSTR2a and -5 in pituitary lesions

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Introduction

Ephrin receptors (EPHs) compose the largest known subfamily of tyrosine kinases receptors and are bound and interact with EPHs-interacting proteins (Ephrins). They have a role in tumor growth, invasion, angiogenesis and metastasis of several neoplasms. Aim of the study was to investigate their expression in pituitary adenomas and their correlation with somatostatin receptor (SSTRs) expression.

Material and Methods

Our study group consisted of 18 patients (9 males with median age 54 and females with median age 59) with pituitary lesions (7 somatotropic and 2 corticotropic adenomas, 8 non-functioning macro-adenomas and 1 resistant prolactionoma).

Formalin fixed-paraffin embedded (FFPE) tissue sections from the lesions were assessed immunohistochemically for EPH-A4, -A5, -B2 and -B5, SSTR2a, SSTR5 and E-cadherin expression were evaluated.

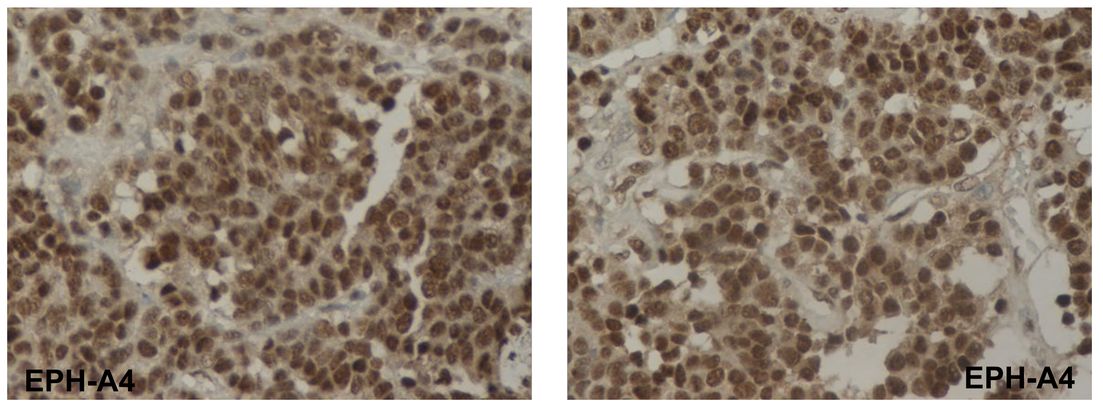
Positivity is defined when >4% of pituitary cells have positive staining, after observation of at least 1000 cells. An immunoreactive score (**IRS**) was created according to the sum of **percentage of EPH-A4, -A5, -B2 and -B5 positivity** (0/negative staining: 0–4% of pituitary cells positive; 1: 5–30% of pituitary cells positive; 2: 31-60% of pituitary cells positive; 3: 61–100% of pituitary cells positive) **and the intensity of staining** (0: negative staining, 1: mild staining; 2: intermediate staining; 3: intense staining). A case was characterized to present low, medium or high EPH expression if the total score was 0-2, 3-4 and 5-6, respectively. The H-score is determined by adding the results of multiplication of the percentage of cells with staining intensity ordinal value (scored from 0 for “no signal” to 3 for “strong signal”) with 300 possible values. SSTRs expression was determined according Volante score.

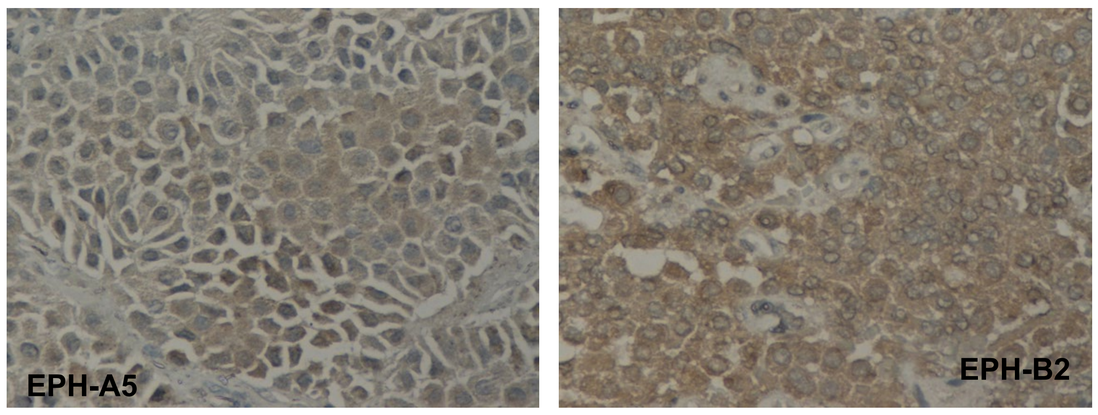
Results

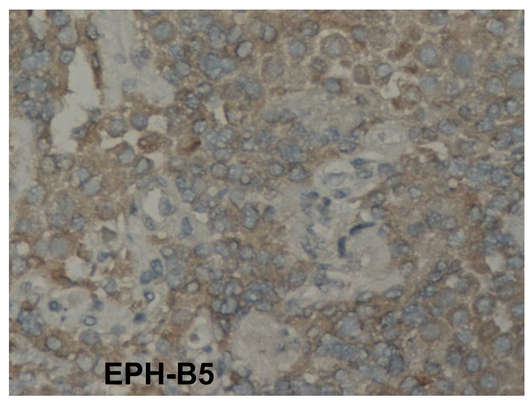
Cytoplasmic and nuclear for EPH-A4 and cytoplasmic for EPH-A5, -B2 and -B4 pattern of immunostaining was noted. Positivity for **EPH-A4** was seen in 17/18 (94%) of the specimens (17/18 with cytoplasmic and 13/18 with nuclear pattern). All corticotropic and somatotropic adenomas found positive for EPH-A4 with both patterns. EPH-A4 IRS was mild for 4, intermediate for 6, intense for 3 cases. Only H-score for EPH-A4 expression was high (range 30-255).Expression of SSTR2a was noted in 6/13 (46%) and of SSTR5 in 4/8 (50%) of specimens. The corticotropic and 80% of somatotropic adenomas (4/5), which expressed SSTR2a showed intermediate and intense staining for EPHA4 with both patterns. All somatotropic (2/2) and corticotropic (2/2) adenomas expressed SSTR5, also expressed EPHA4 with both patterns. None of the NFPAs expressed SSTR2a(5/5) or SSTR5 (4/4) as opposed to EPHA4, which was expressed by 87.5% of NFPA (7/8). Sixty-six percent (2/3) of NFPA, which expressed EPH-A4 expressed also E-cadherin.Positivity for **EPH-A5** and **EPH-B2** was seen in 4/18 (22%) specimens and for **EPH-B4** in 1/18 (5.5%), all non-functioning adenomas with cytoplasmic pattern.

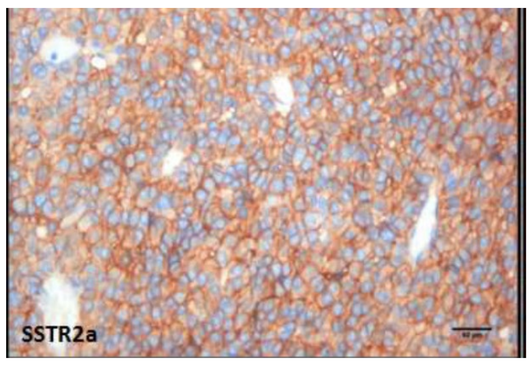
Results

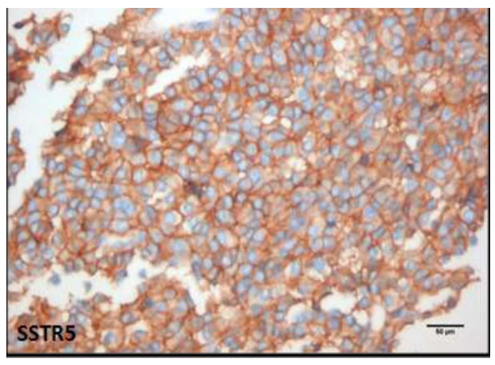
Cytoplasmic and nuclear expression of EPH-A4 and cytoplasmic expression of EPH-A5, EPH-B2, EPH-B4, SSTR2 and STTR5.

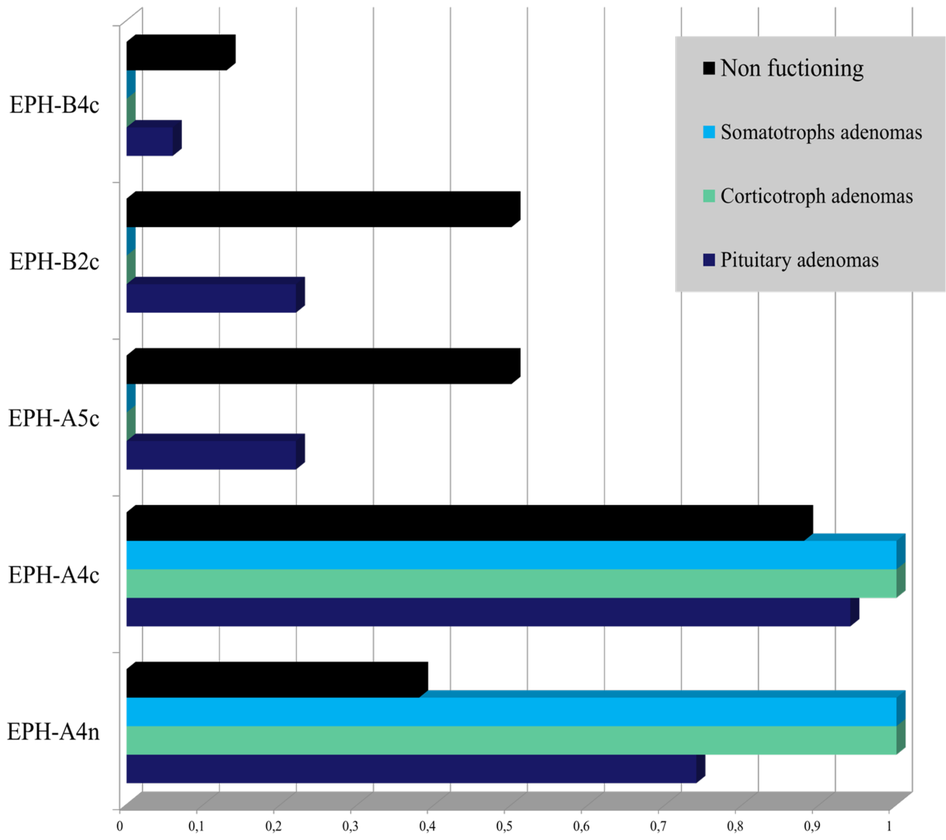












Conclusions

Our data indicate for the first time the increased expression of mainly EPH-A4 and to a lesser extent of EPH-A5, -B2 and -B4 in pituitary lesions. The pattern of co-expression of EPH-A4 with SSTR was seen only in functional pituitary adenomas. Their involvement in the pathophysiology of pituitary lesions requires further investigation to clarify their role and their possible potential prognostic value.