



Is the somatostatin receptor type 5 expression important in resistant prolactinomas?

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Received: 8 October 2025 / Accepted: 9 October 2025

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Agarwal et al. [1] investigated by immunohistochemistry (IHC) the expression patterns of dopamine 2 (D2R), somatostatin 2 (SST2) and 5 (SST5) receptors in the pituitary tissue of 34 patients who underwent surgery for a prolactinoma (PRLoma). Among these patients, 22 displayed dopamine (DA) resistance. As expected, they found that most PRLomas expressed D2R, but also SST5 and SST2 were expressed in 70% and 40% of the tumors, respectively. In addition, the authors investigated the *in vitro* effects of cabergoline, octreotide and pasireotide on prolactin (PRL) production by prolactinoma cells in primary culture and found that DA was more potent than pasireotide and octreotide. The latter compounds were anyway able to significantly inhibit PRL secretion. The authors suggest that targeting SST5 with pasireotide may be a potential treatment modality for further clinical investigation in the treatment of a subset of DA resistant or intolerant prolactinomas.

The 2023 Pituitary Society international Consensus Statement [2] defined DA ‘resistance’ as lack of PRL serum levels normalization or lack of significant tumor shrinkage ($\geq 30\%$ reduction in maximum diameter) under standard DA doses (i.e. cabergoline 2.0 mg/week) for at least 6 months. DA treatment may be successful in controlling PRL levels but not in reducing tumor volume or vice-versa. In previous studies, reduced expression of D2R and estrogen receptor alpha (ER α) has been consistently associated with DA resistance [3]. Until recently, reliable IHC analysis of D2R had not been feasible due to the lack of validated antibodies,

preventing standardized receptor profiling in clinical practice [3]. The study by Agarwal et al. [1] therefore represents a significant step forward, as it provides the largest series of PRLomas investigated for D2R, SST2, and SST5 expression by validated IHC. Their work confirms that D2R can be robustly and reproducibly evaluated in surgical specimens, opening avenues for incorporating D2R immunoprofiling into treatment stratification algorithms.

There is the need for further medical treatment to better address the challenges in the management of patients with DA-resistant PRLomas. In these settings, pasireotide, a SST agonist, may play a role. Indeed, as also reported by Agarwal et al. [1], PRLomas may express SST5 for which pasireotide has the highest affinity. Notably, this study provides evidence that SST receptor expression in PRLomas, though generally lower than in other pituitary adenomas, is not negligible and may have therapeutic relevance. Indeed, while SST receptor profiling has long been standard practice in other pituitary adenomas [4–7], with IHC widely applied for guiding treatment with SST analogues, its role in PRLomas has been underexplored. IHC offers several advantages in this context: it is practical, rapid, and correlates well with mRNA expression levels [8]. Other advantages of IHC include direct visualization of tumor cells and exclusion of endothelial labeling [9]. Nevertheless, despite multiple proposed scoring systems, no universally accepted technique or scoring methodology exists for SST receptors [10].

The potential therapeutic role of pasireotide in aggressive or DA-resistant PRLomas is suggested in previously published case reports and small series [11–13]. A specific subgroup of DA-resistant tumors demonstrates moderate-to-high SST5 expression, and treatment with pasireotide has been associated with clinically significant responses, including also tumor cystic degeneration and necrosis [11–13]. Importantly, these clinical observations raise the possibility that pasireotide may represent a viable therapeutic alternative before escalation to cytotoxic therapies such as temozolomide [14]. This is of particular interest in

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aggressive PRLomas, where therapeutic options are limited and prognosis is poor.

Indeed, PRLoma management is usually based on the escalation to maximally tolerated DA dose and/or surgery for tumor removal or debulking. Radiotherapy is currently considered as an adjuvant therapeutic approach [15]. Upon failure of these approaches, temozolomide treatment may obtain partial remission [16]. Other approaches have been investigated, especially in the settings of aggressive PRLomas, such as immunotherapy with checkpoint inhibitors [17] and targeted therapy with everolimus [18], bevacizumab, lapatinib [19], tamoxifen [20], but also peptide receptor radionuclide treatment [21].

In this context, the incorporation of SST receptor profiling into the clinical assessment of PRLomas may provide an additional layer of therapeutic stratification. Although SST receptor expression in PRLomas is generally lower and more heterogeneous than in other pituitary adenomas, its presence in a subset of PRLomas - particularly SST5 - opens the possibility of targeted therapy with pasireotide. Pasireotide's pharmacological profile, characterized by its broad binding affinity for SST1–3 and SST5, with highest affinity for SST5, makes it an attractive candidate in DA-resistant tumors with demonstrable SST5 expression [1, 11–13].

Nevertheless, several limitations need to be acknowledged. First, the overall prevalence of high SST5 receptor expression in PRLomas remains low, and inter-study variability is significant, likely reflecting differences in methodology, antibodies, and scoring systems [22–25]. Second, while case reports suggest dramatic responses in selected patients, controlled clinical trials evaluating pasireotide in DA-resistant PRLomas are lacking. Third, the side-effect profile of pasireotide, particularly its diabetogenic potential due to inhibition of insulin secretion, must be carefully considered, particularly in younger patients with otherwise long-life expectancy [26].

Future studies should therefore focus on standardizing receptor assessment in PRLomas. Digital pathology and artificial intelligence (AI)-based image analysis tools have been proposed to improve reproducibility and enable objective scoring of receptor expression [27, 28]. Such tools could facilitate the identification of clinically relevant receptor expression thresholds, allowing the integration of IHC profiling into treatment algorithms. However, validation in multicenter international studies will be essential before these approaches can be widely adopted. Consensus on reproducible, clinically applicable scoring systems represents a pressing need [10].

In conclusion, the work of Agarwal et al. [1] represents an important contribution to the field, demonstrating that D2R expression can be reliably assessed by IHC and highlighting the therapeutic relevance of SST5 receptor profiling in PRLomas.

In DA-resistant tumors, particularly those with low D2R and ER α expression, systematic evaluation of SST5 receptor may help identify patients who could benefit from pasireotide before escalation to cytotoxic or experimental therapies. While additional research is required to validate these findings and establish standardized methodologies, this approach offers a rational, systematically driven strategy for addressing one of the most challenging aspects of PRLoma management.

Author contributions Both L.C. and M.C.Z., contributed to literature search and manuscript writing.

Funding This manuscript did not receive specific funding.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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