Thyroid hemiagenesis with primary hyperparathyroidism or papillary thyroid carcinoma: A report of two cases and literature review

Saad M. Alqahtani1 | Sultan Alanesi2 | Yousef Alalawi2

1Department of Surgery, College of Medicine, Majmaah University, Al-Majmaah, Saudi Arabia
2Department of Surgery, King Salman Armed Forces Hospital in the North-Western Region, Tabuk, Saudi Arabia

Abstract
The combination of TH and PHPT or PTC is extremely rare. A better comprehension of the normal anatomy of the thyroid gland and its variations, congenital anomalies, and related pathologies is essential for safe surgical intervention.

KEYWORDS
papillary thyroid carcinoma, parathyroidectomy, primary hyperparathyroidism, thyroid hemiagenesis, thyroidectomy

1 | INTRODUCTION

Thyroid hemiagenesis (TH) is a rare congenital anomaly of the thyroid gland in which one lobe is absent. We present relatively rare combinations of TH with primary hyperparathyroidism (PHPT) and papillary thyroid cancer (PTC). Additionally, a summary of all PubMed-indexed cases of TH associated with PHPT or PTC is provided.

Thyroid hemiagenesis (TH) is the failed embryological development of one thyroid lobe. TH exhibits gender propensity for female predominance, and the left thyroid lobe is most commonly affected.1,2 TH is believed to be an exceptionally unusual developmental anomaly with an estimated prevalence of 0.02%-0.2%.2 Usually, TH is detected incidentally during routine screening or workup of other thyroid diseases. The underlying etiology of this anomaly is unknown; however, genetic factors may play a role in such pathogenesis.3 TH can be associated with some thyroid diseases including hypothyroidism, Grave’s disease, multinodular goiter, chronic thyroiditis, papillary thyroid carcinoma (PTC), and hyperparathyroidism.1

Herein, we present two cases of TH with relatively rare associations. The first case is a right-sided TH in association with contralateral primary hyperparathyroidism (PHPT) and incidental papillary thyroid microcarcinoma (PTMC) in a 36-year-old female patient. The second case is a left-sided TH in association with PTC in a 40-year-old male patient. To the best of our knowledge, this is the first report of such combinations from Saudi Arabia, and the findings of the first case have not been previously reported in the literature. In addition, we provide a summary of all PubMed-indexed published cases of TH in association with PHPT or PTC.

2 | CASE 1

A 36-year-old female patient presented to the surgical clinic with neck swelling for three months. Another systematic review was unremarkable. Physical examination revealed a 2 × 2 cm swelling on the left side of the neck without palpable cervical lymphadenopathy. Laboratory tests demonstrated thyroid-stimulating hormone (TSH) of 2.9 µIU/mL (reference range: 0.5-5.1 µIU/mL), parathyroid hormone (PTH) of 426 pg/mL (reference range: 14-72 pg/mL), serum calcium of 2.18 mmol/L (reference range: 2.1-2.5 mmol/L), and alkaline phosphatase of 131 U/L (reference range: 50-136 U/L).
Neck ultrasound (US) confirmed an absent right thyroid lobe and enlargement of the left thyroid lobe and isthmus. Few nodules were noted on the left thyroid lobe; the largest nodule measured $1.73 \times 0.91$ cm. Computed tomography (CT) of the neck showed a $4.2 \times 2.0$ cm, well-defined, oval-shaped heterogeneously enhanced lesion just posterior to the left thyroid lobe, and lateral to the left side of the trachea. The right thyroid lobe was not visualized (Figure 1A). Nuclear scans localized a parathyroid adenoma at the lower pole of the left thyroid lobe and also confirmed the absence of the right thyroid lobe (Figure 1B). US-guided fine-needle aspiration cytology (FNAC) of the nodule was compatible with benign thyroid.

The intraoperative findings included a right-sided TH, a suspicious multinodular left thyroid lobe with the presence of an isthmus, and a left inferior parathyroid adenoma. In addition, size and position of the other parathyroid glands were normal. Left lobectomy with left inferior parathyroidectomy was performed (Figure 1C and D). The final histopathology showed a $3.5 \times 2.5 \times 1.5$ cm parathyroid adenoma, and a 2 mm PTMC involving the superior pole of the left lobe associated with lymphocytic thyroiditis and multinodular goiter. After parathyroidectomy, the PTH level dropped to 99.9 pg/mL and the frozen section confirmed the diagnosis of PA. On the second postoperative day, the patient was discharged in good health condition. On her follow-up examination in the clinic, the PTH level was 70 pg/mL.

3 | CASE 2

A 40-year-old male patient presented to the surgical clinic complaining of neck swelling for one year. No other complaints were reported. On physical examination, a $2 \times 2$ cm palpable swelling was detected on the right side of the neck. According to the laboratory tests, TSH was 1.5 µIU/mL (reference range: 0.5-5.1 µIU/mL), serum calcium 2.2 mmol/L (reference range:...
| No. | Study                          | Year | Ref  | Age | Sex | Site of TH | Site of PA | TH with PA                                                                 | Type of operation                                      | Size of adenoma                        |
|-----|--------------------------------|------|------|-----|-----|------------|-----------|----------------------------------------------------------------------------|--------------------------------------------------------|----------------------------------------|
| 1   | Maganini and Narendran        | 1977 | [13] | 37  | M   | Lt         | Lt inferior| Ipsilateral                                                                  | Lt lower PTx + resection of the right lower pole of the thyroid mass | 1.5 cm                                 |
| 2   | Woods and Loury                | 1992 | [5]  | 31  | F   | Lt         | Lt superior| Ipsilateral                                                                  | Lt upper PTx                                           | 1.3 × 0.8 × 0.3 cm                     |
| 3   | Duh et al                     | 1994 | [14] | 62  | M   | Lt         | Parathyroid hyperplasia                                                      | Not applicable                                         | Subtotal PTx + bilateral thymectomy       | Rt superior: 1.8 × 1.2 × 1 cm            |
|     |                               |      |      |     |     |            |            |                                                                             |                                                        | Rt inferior: 1 × 1 × 0.5 cm             |
|     |                               |      |      |     |     |            |            |                                                                             |                                                        | Lt superior: 0.8 × 0.4 × 0.3 cm         |
|     |                               |      |      |     |     |            |            |                                                                             |                                                        | Lt inferior: 1.8 × 0.5 × 0.4 cm         |
| 4   | Duh et al                     | 1994 | [14] | 34  | M   | Isthmus    | Parathyroid hyperplasia                                                      | Not applicable                                         | Subtotal PTx + bilateral thymectomy       | Rt superior: 0.9 × 0.7 × 0.3 cm         |
|     |                               |      |      |     |     |            |            |                                                                             |                                                        | Rt inferior: 1.2 × 0.8 × 0.4 cm         |
|     |                               |      |      |     |     |            |            |                                                                             |                                                        | Lt superior: 0.8 × 0.7 × 0.4 cm         |
|     |                               |      |      |     |     |            |            |                                                                             |                                                        | Lt inferior: 1.1 × 0.9 × 0.5 cm         |
| 5   | Sakurai et al                 | 2007 | [6]  | 42  | M   | Rt         | Lt inferior| Contra lateral                                                                | Lt lower PTx                                           | 1.5 × 1 × 1 cm                         |
| 6   | Mydlarz et al                 | 2010 | [15] | 55  | F   | Lt         | Lt superior and inferior                                                    | Ipsilateral                                             | Lt lobectomy + Lt upper and lower PTx   | Lt superior: 2.2 cm                     |
|     |                               |      |      |     |     |            |            |                                                                             |                                                        | Lt inferior: 2.4 cm                     |
| 7   | Isreb et al                   | 2010 | [16] | 75  | F   | Lt         | Lt inferior| Ipsilateral                                                                  | Lt lower PTx                                           | NR                                     |
| 8   | Kroeker et al                 | 2011 | [17] | 41  | M   | Lt         | Lt inferior| Ipsilateral                                                                  | Lt lower PTx                                           | NR                                     |
| 9   | Onci et al                    | 2012 | [18] | 66  | F   | Rt         | Lt inferior: hyperplasia                                                    | Ipsilateral                                             | left lobectomy + Lt lower and             | Lt inferior: NR                        |
|     |                               |      |      |     |     |            |            |                                                                             |                                                        | Rt upper PTx                           |
|     |                               |      |      |     |     |            |            |                                                                             |                                                        | Lt inferior: 1.5 × 0.8 cm               |
| 10  | Ferrari et al                 | 2014 | [9]  | 15  | F   | Lt         | Rt inferior| Contra lateral                                                                | Rt lower PTx                                           | 1.1 × 0.5 × 0.4 cm                     |
| 11  | Eroglu et al                  | 2015 | [19] | 27  | F   | Rt         | Rt         | Ipsilateral                                                                  | PTx                                                    | 2 × 1.1 cm                             |
| 12  | Simsek et al                  | 2015 | [4]  | 49  | F   | Rt & Lt    | Rt inferior| Not applicable                                                                 | Rt lower PTx + isthmusectomy                         | 2 × 1.0 cm                             |
| 13  | Present study                 | 2021 |      | 36  | F   | Lt         | Lt inferior| Contra lateral                                                                | Lt lobectomy + Lt lower PTx                          | 3.5 × 2.5 × 1.5 cm                     |

Abbreviations: F: female; Lt: left; M: male; No: number; NR: not reported; PA: parathyroid adenoma; PTx: parathyroidectomy; Ref: reference; Rt: right; TH: thyroid hemiagenesis.
2.1-2.5 mmol/L), thyroglobulin assay 0.1 ng/mL (reference range: 3.5-77 ng/mL), and thyroglobulin antibody 26.3 IU/mL (reference range: 0-115 IU/mL).

US of the neck showed a normal-sized right thyroid lobe containing an ill-defined hypoechoic, hypervascular focal lesion measuring 1.2 × 0.7 cm. In addition, the isthmus was normal and the left thyroid lobe was not visualized. No significant cervical lymphadenopathy was noted. US-guided FNAC of the right thyroid lobe nodule was suggestive of PTC.

Intraoperatively, a normal-appearing isthmus, a left-sided TH, and a right thyroid lobe nodule were identified (Figure 2). The patient underwent total thyroidectomy, and the final histopathology confirmed PTC associated with Hashimoto’s thyroiditis. The postoperative course was uneventful. FIGURE 2 Intraoperative image showing the right lobe with isthmus

4 | DISCUSSION

TH is an uncommon embryological disorder of the thyroid gland. It was first reported by Handsfield-Jones in 1866.1 Anatomically, TH usually affects the left side of the thyroid gland. The isthmus is present in 50% of all TH patients, with a distinctive hockey stick sign-on scintigraphic imaging.1 Epidemiologically, TH exhibits gender predilection for females. Budny et al proposed that TH could be linked to various genetic mutations involving thyroid transcription factors and proteasome-related genes.3 Herein, we reported two cases of TH. The first case described a female patient with a right-sided TH, whereas the second case described a male patient with a left-sided TH; the isthmus was present in both cases.

Thyroid agenesis may involve both lobes, one lobe, or the isthmus.4 In contrast to ectopic thyroid where there is a failure of thyroid descent, hemiagenesis results from the inability of the thyroid to split into two separate lobes.5,6

TH usually does not lead to specific symptoms. Rather, TH is often detected incidentally during screening or workup of other thyroid diseases.7-9 In the cases reported here, both patients exhibited symptoms. Moreover, Case 1 was associated with parathyroid adenoma, whereas Case 2 was accompanied by PTC.

Most patients with TH are euthyroid, as noted in our reported patients. High TSH can result in diffuse or nodular goiter and increase the probability of neoplastic transformation

**TABLE 2** A summary of all PubMed-indexed case reports about thyroid hemiagenesis in association with thyroid cancer

| No | Study         | Year | Ref  | Age | Sex | Site of Cancer | Site of TH | Type of thyroid cancer                        |
|----|---------------|------|------|-----|-----|----------------|------------|-----------------------------------------------|
| 1  | Hamburger et al | 1970 | [21] | 14 F |     | Rt lobe        | Lt         | Papillary + follicular                        |
| 2  | Harada et al  | 1972 | [22] | 74 F |     | Lt lobe        | Rt         | Papillary                                    |
| 3  | Greening et al | 1980 | [23] | 51 F |     | Rt lobe        | Lt         | Papillary                                    |
| 4  | Khatri et al  | 1992 | [24] | 41 F |     | Lt lobe        | Rt         | Papillary                                    |
| 5  | McHenry et al | 1995 | [25] | 58 F |     | Rt lobe        | Lt         | Follicular                                   |
| 6  | Shaha et al   | 1997 | [26] | 30 F |     | Lt lobe        | Rt         | Papillary                                    |
| 7  | Huang et al   | 2002 | [7]  | 47 F |     | Lt lobe        | Rt         | Papillary                                    |
| 8  | Pizzini et al | 2005 | [20] | 54 M |     | Rt lobe        | Lt         | Papillary                                    |
| 9  | Ammaturo et al| 2007 | [27] | 39 F |     | Rt lobe        | Lt         | Papillary                                    |
| 10 | Lee et al     | 2008 | [28] | 69 F |     | Rt lobe        | Lt         | Papillary                                    |
| 11 | Canani et al  | 2008 | [29] | 35 F |     | Thyroglossal duct | Rt       | Papillary cancer of Thyroglossal duct cyst |
| 12 | Wang et al    | 2014 | [8]  | 49 F |     | Lt lobe        | Rt         | Medullary                                    |
| 13 | Wang et al    | 2014 | [8]  | 60 F |     | Rt lobe        | Lt         | Papillary                                    |
| 14 | Karatag et al | 2013 | [11] | 59 F |     | Rt lobe        | Lt         | Papillary                                    |
| 15 | Vayisoglu et al | 2013 | [30] | 43 F |     | Lt lobe        | Isthmus    | Papillary                                    |
| 16 | Campenni et al| 2015 | [31] | 36 M |     | Rt lobe        | Lt         | Papillary                                    |
| 17 | Rajbhandari et al | 2016 | [32] | 28 M |     | Rt lobe        | Isthmus    | Papillary                                    |
| 18 | Sato et al    | 2017 | [2]  | 64 F |     | Nodule on the site of absent lobe | Lt       | Papillary + poorly differentiated thyroid carcinoma |
| 19 | Ugur et al    | 2019 | [33] | 54 F |     | Both lobes     | Isthmus    | Papillary                                    |
| 20 | Present study [Case 2 ] | 2021 |      | 40 M |     | Rt lobe        | Lt         | Papillary                                    |
| 21 | Present study [Case 1] | 2021 |      | 36 F |     | Lt lobe        | Rt         | PTMC                                         |

Abbreviations: F: female; Lt: left; M: male; No: number; PTMC: papillary thyroid microcarcinoma; Ref: reference; Rt: right; TH: thyroid hemiagenesis.
and thyroid cancer. Thus, TSH levels should be closely monitored in TH patients in which surgical interventions are not indicated.10

Earlier studies investigated the role of neck US in the assessment of TH. Neck US is a well-accepted and cost-effective investigational tool. Herein, it confirmed the TH diagnosis in our patients and this was in accordance with what had been reported previously.7,11

Thyroid scintigraphy is helpful in detecting ectopic thyroid and other diseases.12 However, this radiological investigation may be misleading. Therefore, further investigations, such as CT and magnetic resonance imaging along with neck US, can aid in establishing the definitive diagnosis.1,7,11

The combination of TH and PHPT is extremely rare. Only 12 cases have been reported to date in the English-language PubMed-indexed literature (Table 1).4-6,9,13-19 Out of 12 patients, five (42%) were males and seven (58%) were females. The ages of patients ranged from 15 to 75 years. Our Case 1 report is unique; we describe a female patient with rightsided TH in addition to contralateral parathyroid adenoma and incidental PTMC involving the left thyroid lobe. This association has never been published before in the English language PubMed-indexed literature.

The co-occurrence of TH and thyroid cancer is quite a rare condition. So far, 19 cases have been documented in the PubMed-indexed literature (Table 2).2,7,8,11,20-33 The ages of patients ranged from 14 to 74 years. Only three patients were males (16%), while the majority were females (n = 16, 84%). Including our two cases, 16 cases were associated with PTC, one with medullary thyroid cancer, one with follicular thyroid cancer (FTC), one with both PTC and FTC, and one with PTC and poorly differentiated thyroid carcinoma. The remaining case showed PTMC. Our Case 2 is a male patient with left-sided TH in association with PTC affecting the right lobe. This is the third-reported case in the PubMed-indexed literature with such combinations.

Being a rare condition, management is individualized and depends on the accompanying pathological diseases in the remaining lobe.28

In conclusion, based on literature review, only few cases of TH related to PTC or PHPT have been reported. Furthermore, no correlation was identified between the TH and PHPT sites (contralateral vs. ipsilateral), implying separate embryological origins. A better comprehension of the normal anatomy of the thyroid gland and its variations, congenital anomalies, and related pathologies is important for safe surgical intervention and better outcomes.

ACKNOWLEDGMENTS

Authors would like to acknowledge Prof. Dr Saif Alsobhi for his valuable inputs in reviewing the manuscript. Published with written consent of the patient.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

SMA, SA, and YA: substantially contributed to study conception and design, acquisition of data, analysis and interpretation of data, and clinical management of patients; SMA: drafted the article; SA and YA: revised manuscript critically for important intellectual content; All authors: read and approved the version to be published; SMA: acted as the guarantor for the content.

CONSENT

Informed consent was obtained from both patients.

RESEARCH INVOLVING HUMAN PARTICIPANTS

Informed consent was obtained from both patients.

DATA AVAILABILITY STATEMENT

All data are available in the manuscript.

ORCID

Saad M. Alqahtani https://orcid.org/0000-0002-2198-7970

REFERENCES

1. Melnick JC, Stemkowski PE. Thyroid hemiagenesis (hockey stick sign): a review of the world literature and a report of four cases. J Clin Endocrinol Metab. 1981;52:247-251.
2. Sato H, Tsukahara K, Motohashi R, Wakiya M, Serizawa H, Kurata A. Thyroid Carcinoma on the Side of the Absent Lobe in a Patient with Thyroid Hemiagenesis. Case Rep Otolaryngol. 2017:2017;4592783.
3. Budny B, Szczerpanek-Parul ska E, Zemojtel T, et al. Mutations in proteasome-related genes are associated with thyroid hemiagenesis. Endocrine. 2017;56:279-285.
4. Şimşek T, Cantürk NZ, Cantürk Z, Gürbüz Y. Bilobar thyroid agenesis with primary hyperparathyroidism: report of a case. Surg Today. 2015;45:787-792.
5. Woods RH, Loury M. Thyroid hemiagenesis in a patient with a parathyroid adenoma. Otolaryngol Head Neck Surg. 1992;107:469-471.
6. Sakurai K, Amano S, Enomoto K, Matsuo S, Kitajima A. Primary hyperparathyroidism with thyroid hemiagenesis. Asian J Surg. 2007;30:151-153.
7. Huang S-M, Chen H-D, Wen TY, Kun M-S. Right thyroid hemiagenesis associated with papillary thyroid cancer and an ectopic prelaryngeal thyroid: a case report. J Formos Med Assoc. 2002;101:368-371.
8. Wang J, Gao L, Song C. Thyroid hemiagenesis associated with medullary or papillary carcinoma: report of cases. Head Neck. 2014;36:E106-E111.
9. Ferrari CC, Lorenz K, Dionigi G, Dralle H. Surgical strategy for primary hyperparathyroidism with thyroid hemiagenesis. Langenbecks Arch Surg. 2014;399:1077-1081.
10. Haymart MR, Repplinger DJ, Leversone GE, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is
associated with greater risks of differentiated thyroid cancer and advanced tumor stage. *J Clin Endocrinol Metab.* 2008;93:809-814.

11. Karatağ GY, Albayrak ZK, Önay HK, Karatağ O, Peker Ö. Coexistence of thyroid hemiagenesis, nodular goitre and papillary carcinoma. *Kulak Burun Bogaz Ihtis Derg.* 2013;23:115-118.

12. De Remigis P, D’Angelo M, Bonaduce S, Giandomenico VD, Sensi S. Comparison of ultrasonic scanning and scintiscanning in the evaluation of thyroid hemiagenesis. *J Clin Ultrasound.* 1985;13:561-563.

13. Maganini R, Narendran K. Hyperparathyroidism in a patient with thyroid hemiagenesis. *IMJ Ill Med J.* 1977;151:368-370.

14. Duh Q-Y, Ciulla TA, Clark OH. Primary parathyroid hyperplasia associated with thyroid hemiagenesis and agenesis of the isthmus. *Surgery.* 1994;115:257-263.

15. Mydlarz WK, Zhang K, Micchelli S, Kim M, Tufano RP. Ipsilateral double parathyroid adenoma and thyroid hemiagenesis. *ORL J Otorhinolaryngol Relat Spec.* 2010;72:272-274.

16. Isreb S, Alem F, Smith D. Left thyroid hemiagenesis in a patient with primary hyperparathyroidism. *BMJ Case Rep.* 2010;2010:bcr0320102864.

17. Kroeker TR, Stancoven KM, Preskitt JT. Parathyroid adenoma on the ipsilateral side of thyroid hemiagenesis. *Proc (Bayl Univ Med Cent).* 2011;24:92-93.

18. Oruci M, Ito Y, Buta M, et al. Right thyroid hemiagenesis with adenoma and hyperplasia of parathyroid glands-case report. *BMC Endocr Disord.* 2012;12:29.

19. Eroglu M, Ozkul F, Barutcu EC, et al. Severe hyperparathyroidism in a patient with right thyroid hemiagenesis. *J Pak Med Assoc.* 2015;65:1022-1023.

20. Pizzini A, Papi G, Corrado S, Carani C, Roti E. Thyroid hemiagenesis and incidentally discovered papillary thyroid cancer: case report and review of the literature. *J Endocrinol Invest.* 2005;28:66-71.

21. Hamburger JI, Hamburger SW. Thyroidal hemiagenesis: Report of a case and comments on clinical ramifications. *Arch Surg.* 1970;100:319-320.

22. Harada T, Nishikawa Y, Ito K. Aplasia of one thyroid lobe. *Am J Surg.* 1972;124:617-619.

23. Greening W, Sarker S, Osborne M. Hemiagenesis of the thyroid gland. *Br J Surg.* 1980;67:446-448.

24. Khatri VP, Espinosa MH, Harada WA. Papillary adenocarcinoma in thyroid hemiagenesis. *Head Neck.* 1992;14:312-315.

25. McHenry CR, Walfish PG, Rosen IB, Lawrence AM, Paloyan E. Congenital thyroid hemiagenesis. *Am Surg.* 1995;61:634-638.

26. Shah A, Gujarati R. Thyroid hemiagenesis. *J Surg Oncol.* 1997;65:137-140.

27. Amnaturo S, Cerrato C, Duraccio S, et al. Thyroid hemiagenesis associated with Flajani’s disease and papillary carcinoma. *A case report. Chir Ital.* 2007;59:263-267.

28. Lee YS, Yun J-S, Jeong JJ, Nam K-H, Chung WY, Park CS. Thyroid hemiagenesis associated with thyroid adenomatous hyperplasia and papillary thyroid carcinoma. *Thyroid.* 2008;18:381-382.

29. Canani FB, Dall'Olio D, Chiarini V, Casadei GP, Papini E. Papillary carcinoma of a thyroglossal duct cyst in a patient with thyroid hemiagenesis: effectiveness of conservative surgical treatment. *Endocr Pract.* 2008;14:465-469.

30. Vayisoglu Y, Ozcan C, Gen R, Eti CM, Sut H, Gorur K. Thyroid isthmus agenesis associated with thyroid papillary carcinoma in patients with thyroid hemiagenesis. *J Craniofac Surg.* 2013;24:e428-e429.

31. Campenni A, Giovinazzo S, Curti L, et al. Thyroid hemiagenesis, Graves’ disease and differentiated thyroid cancer: a very rare association: case report and review of literature. *Hormones (Athens).* 2015;14:451-458.

32. Rajbhandari P, Shrestha B, Dhakal A, Amatya R. Thyroid isthmus agenesis in a patient with papillary carcinoma of thyroid. *Kathmandu Univ Med J (KUMJ).* 2016;56:368-370.

33. Ugur K, Sevgi K, Tugrul K, Sengul D. Agenesis of isthmus of thyroid gland in the presence of ectopic thyroid tissue associated with papillary carcinoma. *J Coll Physicians Surg Pak.* 2019;29:75-77.

How to cite this article: Alqahtani SM, Alanesi S, Alalawi Y. Thyroid hemiagenesis with primary hyperparathyroidism or papillary thyroid carcinoma: A report of two cases and literature review. *Clin Case Rep.* 2021;9:1615–1620. [https://doi.org/10.1002/ccr3.3856](https://doi.org/10.1002/ccr3.3856)