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Vertebral Venous Congestion That May Mimic Vertebral Metastasis on Contrast-Enhanced Chest Computed Tomography in Chemoport Inserted Patients

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Objective: This study aimed to determine the prevalence of vertebral venous congestion (VVC) in patients with chemoport insertion, evaluate the imaging characteristics of nodular VVC, and identify the factors associated with VVC.

Materials and Methods: This retrospective single-center study was based on follow-up contrast-enhanced chest computed tomography (CT) of 1412 adult patients who underwent chemoport insertion between January 2016 and December 2016. The prevalence of venous stenosis, reflux, and VVC were evaluated. The imaging features of nodular VVC, including specific locations within the vertebral body, were analyzed. To identify the factors associated with VVC, patients with VVC were compared with a subset of patients without VVC who had been followed up for > 3 years without developing VVC after chemoport insertion. Toward this, a multivariable logistic regression analysis was performed.

Results: After excluding 333 patients, 1079 were analyzed (mean age ± standard deviation, 62.3 ± 11.6 years; 540 females). The prevalence of VVC was 5.8% (63/1079), with all patients (63/63) demonstrating vertebral venous reflux and 67% (42/63) with innominate vein stenosis. The median interval between chemoport insertion and VVC was 515 days (interquartile range, 204–881 days). The prevalence of nodular VVC was 1.5% (16/1079), with a mean size of 5.9 ± 3.1 mm and attenuation of 784 ± 162 HU. Nodular VVC tended to be located subcortically. Forty-four patients with VVC underwent CT examinations with contrast injections in both arms; the VVC disappeared in 70% (31/44) when the contrast was injected in the arm contralateral to the chemoport site. Bevacizumab use was independently associated with VVC (odds ratio, 3.45; $P < 0.001$).

Conclusion: The prevalence of VVC and nodular VVC was low in patients who underwent chemoport insertion. Nodular VVC was always accompanied by vertebral venous reflux and tended to be located subcortically. To avoid VVC, contrast injection in the arm contralateral to the chemoport site is preferred.

Keywords: Vertebral venous congestion; Chemoport; Chest CT; Vanishing bone metastasis

INTRODUCTION

Chemoports are implantable central venous access devices widely used for the delivery of chemotherapeutic drugs to cancer patients. However, chemoport-related venous thrombosis or stenosis may occur, which can eventually lead to life-threatening pulmonary embolisms and delay cancer treatment [1,2]. Thrombotic complications of chemoport occur by two different mechanisms: stenosis or occlusion of the accessed vein due to trauma to the venous wall or thrombus formation around the catheter tip [3,4]. The incidence of venous stenosis associated with peripherally inserted central catheters or chemoports is reported to be 7% [5].

Various venous collateral pathways may develop to maintain venous drainage in patients with venous stenosis [6,7]. When venous obstruction occurs in the superior vena cava (SVC) or above, paravertebral collateral pathways can possibly cause vertebral venous congestion (VVC), which

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Korean Journal of Radiology
KJR

may be difficult to distinguish from sclerotic metastasis on contrast-enhanced computed tomography (CT) [8]. This phenomenon has been reported in the literature as a vanishing bone metastasis. As per previous studies, the causes of VVC include SVC obstruction due to chest tumors (direct invasion or extrinsic compression), intravascular catheters (central venous catheters, pacemakers, etc.), trauma, mediastinal fibrosis [8-10], and extrinsic compression of the left innominate vein between the sternum and aortic arch [11,12].

To our knowledge, the factors associated with VVC in patients with chemoport insertion have not been investigated. Given that venous stenosis can result from the partial lysis and recanalization of venous thrombosis [13], there may be a potential association between the risk factors for chemoport-related thrombosis and VVC. The known risk factors for chemoport-related thrombosis include a history of chemoport insertion or chemoport-related thrombosis, repeated attempts of chemoport insertion, and several catheter characteristics (material and tip position) [14-17]. Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF) [18], has been reported as a risk factor for chemoport-related thrombosis in patients with colorectal cancer [19].

This study aimed to determine the prevalence of VVC in patients with chemoport insertion, evaluate the imaging characteristics of nodular-type VVC, which may simulate sclerotic metastasis, and identify factors associated with VVC.

MATERIALS AND METHODS

This retrospective study was approved by Asan Medical Center Institutional Review Board, and the requirement for informed consent was waived (IRB No. 2022-0310).

Patients

All consecutive adult patients who underwent chemoport insertion at our institution between January 1, 2016, and December 31, 2016, were screened for the study, regardless of their cancer type or chemotherapy regimen. The exclusion criteria were as follows: 1) patients with innominate vein stenosis prior to chemoport insertion (n = 9); 2) patients who did not undergo contrast-enhanced chest CT after chemoport insertion (n = 307); and 3) patients with indeterminate lesions that did not conform to the definition of VVC (n = 17). Finally, the study included 1079 patients (Fig. 1).

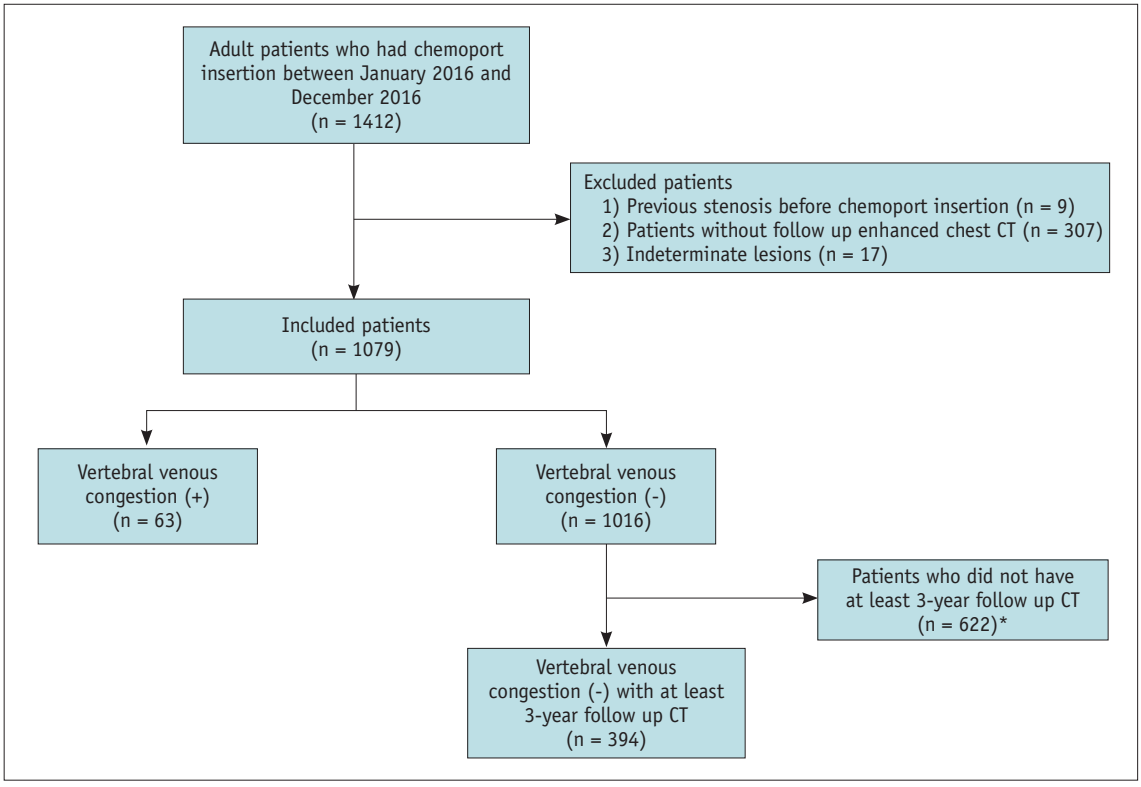

Fig. 1. Flowchart depicting patient selection. These were excluded from the subgroup analysis to identify factors associated with vertebral venous congestion (asterisk). CT = computed tomography

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For the subgroup study to identify the factors associated with VVC, 622 patients who did not have VVC and were followed-up for < 3 years after chemoport insertion were excluded. The control group required considerable observation time because it could take a long time for VVC to occur. A three-year observation period was considered appropriate because it was longer than the upper quartile interval (881 days) between chemoport insertion and VVC.

Data on clinical variables such as age, sex, cancer type, and history of bevacizumab use were collected from medical records. In the subgroup for identifying factors associated with VVC, additional data were collected. These included body mass index (BMI), smoking history (pack-year), hypertension, diabetes, hyperlipidemia, cardiovascular disease, liver function abnormality, dipstick test for albuminuria, history of prior chemotherapy, history of prior central line insertion, and history of prior thromboembolism.

Contrast-Enhanced Chest CT Acquisition

Most patients (85%) underwent follow-up chest CT using a 16-channel CT (SOMATOM Definition AS and Sensation-16; Siemens Healthineers). The settings were as follows: 120 kVp, 150–200 mAs; pitch of 0.875–1, and collimation, 1–1.25 mm. All reconstructions were performed using a B50f kernel with a 1 mm/3 mm/5 mm slice thickness. The scan coverage was from the thoracic inlet to the base of the lungs. Enhanced chest CT images were obtained 50 seconds after the initiation of the intravenous contrast injection (100 mL) at a rate of 3 mL/sec. All CT data were acquired at full inspiration with patients in the supine position. The remaining 15% of patients underwent pulmonary embolism CT or contrast-enhanced chest CT at another hospital and though the specific details of scan protocols were not available, the images seemed to have been obtained at contrast-enhanced phases, similar to those at our institution.

Definition of Venous Stenosis, Venous Reflux, Vertebral Congestion, and Analysis

Innominate vein stenosis was defined as positive when the cross-sectional area of the innominate vein was smaller than that of the carotid artery on the axial images and not due to an external mass effect (Fig. 2A). Vertebral venous reflux was defined as contrast reflux to the paravertebral and/or transforaminal areas of at least three

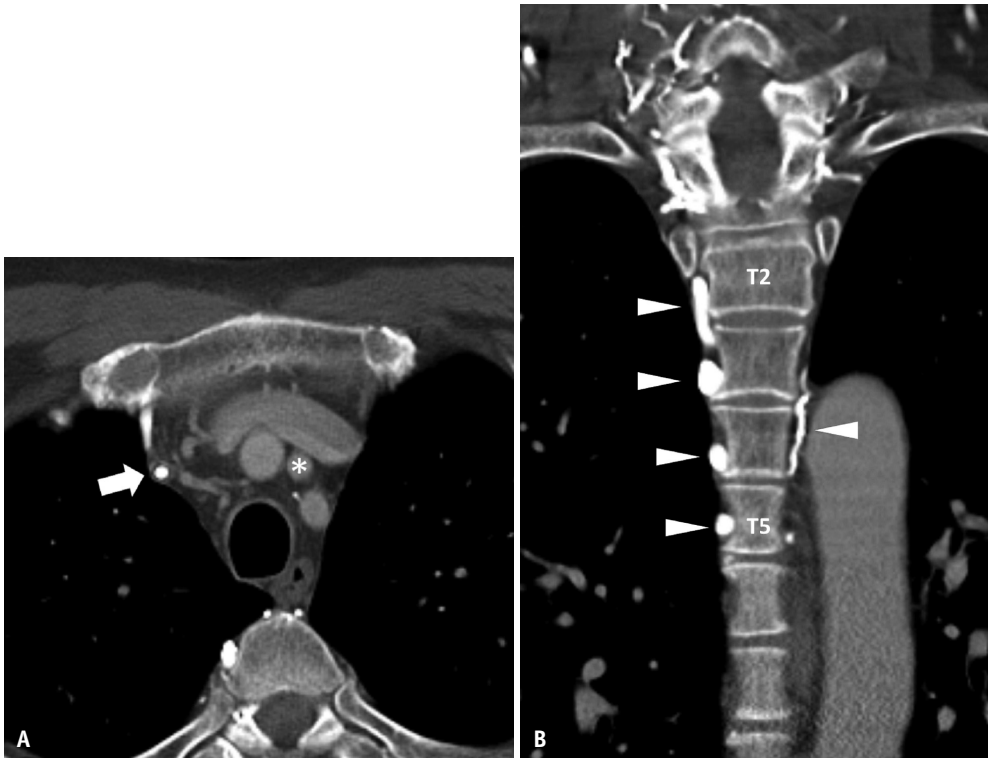

Fig. 2. 57-year-old male with rectal cancer. **A:** Axial contrast-enhanced CT scan shows stenosis of the right innominate vein (white arrow), of which the cross-sectional area is smaller than that of the carotid artery (asterisk). **B:** Coronal contrast-enhanced CT scan shows vertebral venous reflux (white arrowheads) along the T2–5 level, which is defined as contrast reflux to the paravertebral and/or transforaminal areas of at least three spinal levels. CT = computed tomography

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Korean Journal of Radiology
KJR

spinal levels (Fig. 2B). VVC was defined as a focal lesion with a density roughly equivalent to that of the contrast agent in the vertebral body due to collateral venous reflux. Disappearance of the lesion was confirmed on follow-up non-contrast CT, magnetic resonance imaging (MRI), positron emission tomography (PET)/CT, or bone single-positron emission computed tomography (SPECT) (Fig. 3). If the lesion temporarily existed at a single time point, then disappearance or even reappearance during the follow-up enhanced chest CT was also considered VVC (Fig. 4).

The contrast-enhanced chest CT along with medical records were used to identify the site of chemoport insertion and the extremities into which the contrast agent was injected. The presence and level of vein stenosis, as well as the presence of vertebral venous reflux and VVC, were recorded for each patient. In patients with VVC, the vertebral level and VVC configuration were analyzed. This was classified as nodular or linear branching types (Fig. 5). For patients with multiple VVCs, we defined in a patient level as having a nodular VVC if every lesion purely manifested as nodular VVC, and vice versa for the linear-branching type. If the patient had both nodular and linear-branching type we classified the patient as having mixed VVC.

For nodular VVC, which may mimic sclerotic metastasis and therefore termed "vanishing bone metastasis" in the literature, we analyzed the specific location and frequency of the involved vertebral body as well as the size and attenuation of the lesion.

Statistical Analysis

The prevalence of VVC, innominate vein stenosis, and vertebral reflux were determined. The descriptive statistics of the study participants are presented as mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. The association between VVC and innominate vein stenosis, as well as between VVC and vertebral venous reflux, was determined using Pearson's chi-square test.

Logistic regression analyses were performed to identify the factors associated with VVC by comparing patients with VVC to those without VVC who had been followed up for > 3 years without developing VVC after chemoport insertion. Significant variables from univariable logistic regression were included in the multivariable logistic

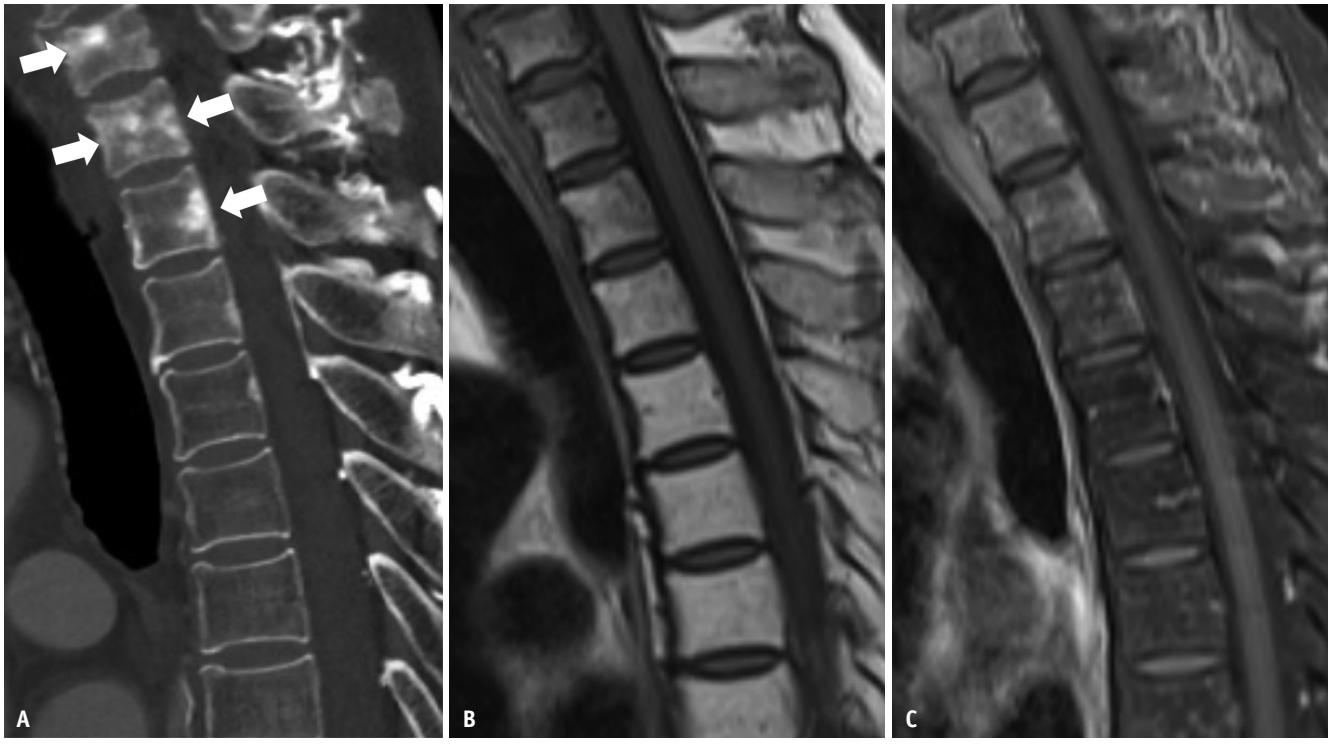

Fig. 3. 60-year-old male with rectal cancer. **A:** The follow-up sagittal chest CT scan shows multifocal nodular high-density lesions (white arrows) at C7–T2 vertebral bodies. Contrast material was injected via the chemoport-inserted side. **B, C:** Sagittal T1WI **(B)** and enhanced T1WI **(C)** magnetic resonance imaging scan (3-month interval) show no apparent nodular enhancing lesion. CT = computed tomography, T1WI = T1-weighted image

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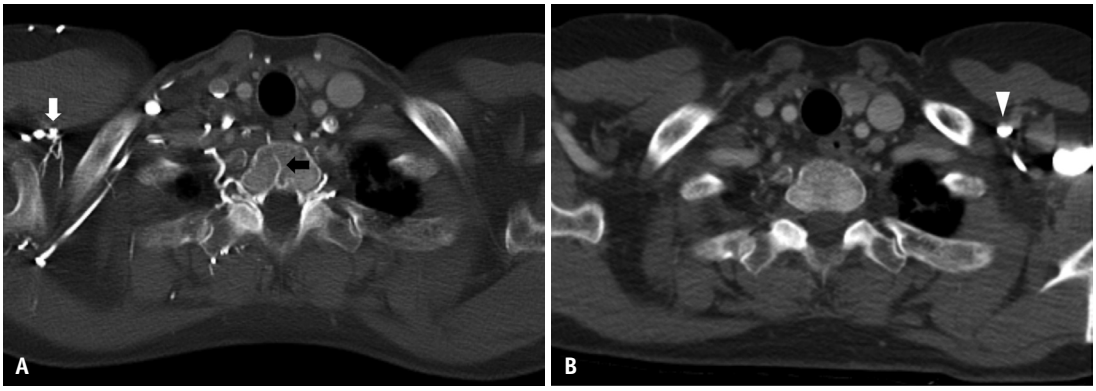

Fig. 4. 51-year-old female with colon cancer and vertebral venous congestion. **A:** Axial enhanced chest CT scan, in which contrast media was injected via the chemoport site (white arrow), shows a focal linear-branching high-density lesion (black arrow) roughly equivalent to that of the contrast agent at the T1 vertebral body. **B:** Follow-up CT scan (6-month interval) with contrast media injection contralateral to the chemoport site (white arrowhead) shows the disappearance of the lesion. CT = computed tomography

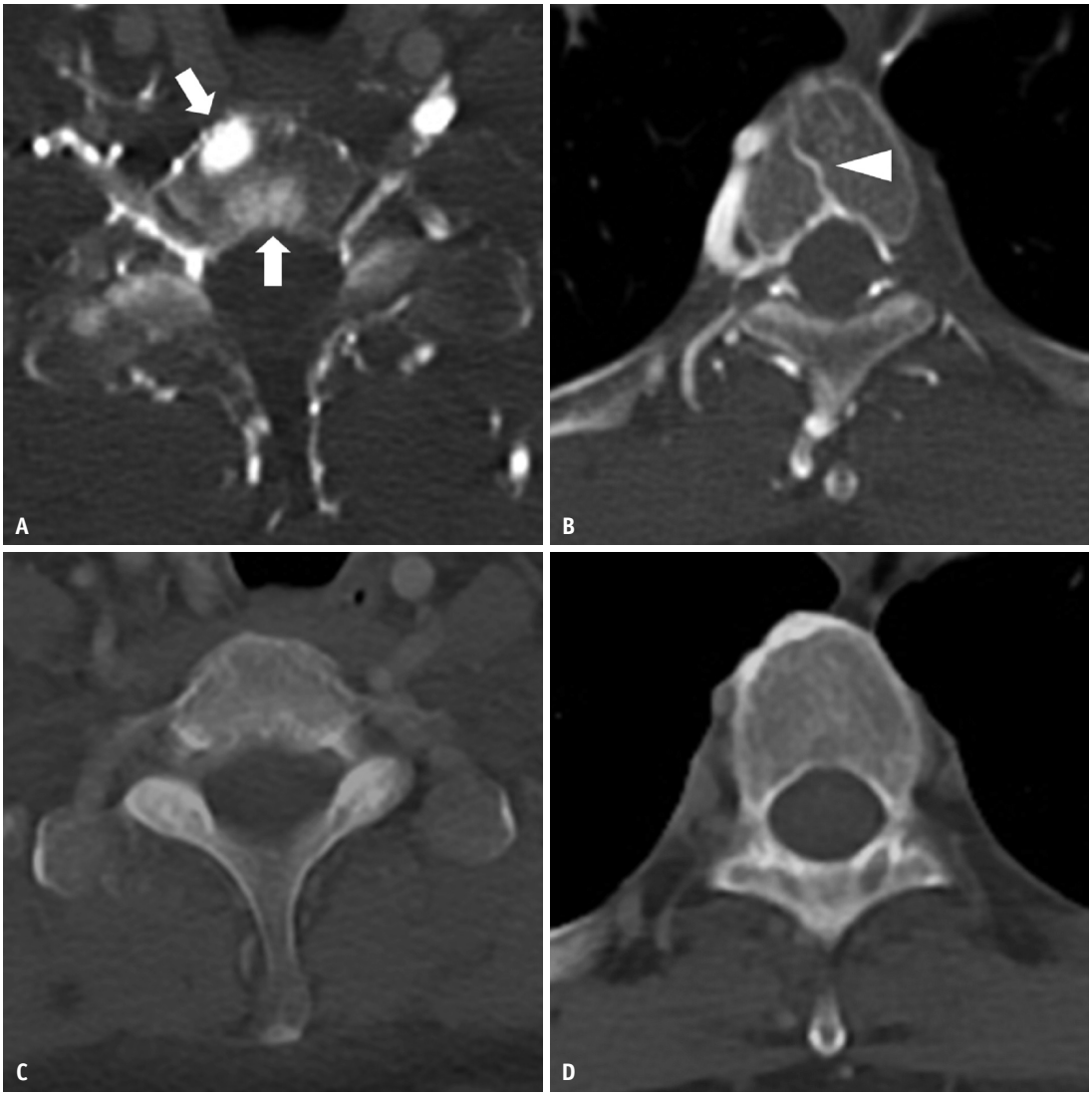

Fig. 5. Morphologic patterns of vertebral venous congestion (VVC). **A, B:** Axial enhanced chest CT scan shows two nodular VVCs (white arrows) at the C7 vertebral body **(A)** and linear-branching VVC (white arrowhead) at the T4 vertebral body **(B)**. **C, D:** Follow-up CT scan (4-month interval) showing the disappearance of the lesion. CT = computed tomography

https://doi.org/10.3348/kjr.2023.0224

Korean Journal of Radiology
KJR

regression analysis. *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using STATA, version 16 (StataCorp).

RESULTS

A total of 1079 patients (mean age ± SD, 62.3 ± 11.6 years; 540 females) were included in the study. All patients had a history of cancer, with colorectal cancer (65.3% [705/1079]) being the most common (Table 1). Notably, 36.3% (392/1079) of the patients received bevacizumab infusions through the chemoport at least once.

The prevalence of VVC and innominate vein stenosis was 5.8% (63/1079, 95% confidence interval [CI]: 4.5%–7.4%) and 8.2% (88/1079, 95% CI: 6.6%–10.0%), respectively. VVC was confirmed by the disappearance of the lesion on follow-up enhanced chest CT (n = 42), whole-body PET/CT (n = 16), non-contrast chest CT (n = 4), and bone SPECT (n = 1). The median time interval between chemoport insertion and VVC was 515 days (interquartile range, 204–881 days). All patients with VVC had vertebral venous reflux, and 67% (42/63, 95% CI: 53.7%–78.0%) had innominate vein stenosis. Except for two patients, VVC occurred exclusively at the cervical or upper thoracic vertebrae (97% [61/63]). The types of VVC observed were as follows: nodular (n = 16, 25%), linear-branching (n = 21, 33%), and mixed (n = 26, 41%). Additional characteristics of VVC in each patient are shown in Supplementary Table 1. Forty-four patients with VVC had CT examinations obtained after contrast injections in both right and left arms. VVC was not visible in 70% (31/44, 95% CI: 55%–83%) of patients when the contrast was injected in the arm contralateral to the chemoport site.

The prevalence of nodular VVC in patients with a chemoport was 1.5% (16/1079, 95% CI: 0.8%–2.4%). The imaging characteristics of nodular VVC are summarized in Table 2. A total of 43 nodular-enhancing lesions were observed in 16 patients with nodular VVC. The mean size of the nodular VVC was 5.9 ± 3.1 mm, and the mean attenuation was 784 ± 162 HU. The specific locations of the epicenters of the nodular VVC in the vertebral body are shown in Figure 6. Most nodular VVCs were located in the subcortical area of the mid-posterior vertebral body (33% [14/43]), followed by the right anterior aspect (21% [9/43]). No lesions were observed on the left anterior or mid-vertebral bodies.

The prevalence of vertebral venous reflux was 15.2%

Table 1. Patient baseline demographic and clinical characteristics

Characteristics	All patients (n = 1079)	Patients with vertebral venous congestion (n = 63)	Patients without vertebral venous congestion (n = 1016)
Age, yr	62.3 ± 11.6	62.4 ± 9.7	62.3 ± 11.7
Sex			
Female	540 (50.0)	23 (37)	517 (50.9)
Male	539 (50.0)	40 (63)	499 (49.1)
Cancer			
Colorectal cancer	705 (65.3)	50 (79)	655 (64.5)
Pancreas cancer	84 (7.8)	4 (6)	80 (7.9)
Breast cancer	61 (5.7)	5 (8)	56 (5.5)
Sarcoma	43 (4.0)	3 (5)	40 (3.9)
Tubo-ovarian cancer	34 (3.2)	0	34 (3.3)
Gastric cancer	31 (2.9)	0	31 (3.1)
Lung cancer	25 (2.3)	0	25 (2.5)
Bile duct cancer	18 (1.7)	1 (2)	17 (1.7)
Gallbladder cancer	12 (1.1)	0	12 (1.2)
Cervical cancer	12 (1.1)	0	12 (1.2)
Others*	54 (5.0)	0	54 (5.3)
Bevacizumab usage	392 (36.3)	36 (57)	356 (35.0)

Data are described as mean ± standard deviation or the number of patients with the percentage in parentheses.
*Adrenal cortical carcinoma, anal squamous carcinoma, pilocytic astrocytoma, combined hepatocellular carcinoma and cholangiocarcinoma, duodenal cancer, neuroendocrine tumor, endometrial cancer, hepatocellular carcinoma, ileal cancer, gastrointestinal stromal tumor, lymphoma, multiple myeloma, primary peritoneal carcinoma, renal cell carcinoma, transitional cell carcinoma, thymic carcinoma, uterine cancer, vaginal cancer, and vulvar cancer

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(164/1079, 95% CI: 13.1%–17.5%). Patients with vertebral venous reflux presented with innominate vein stenosis (n = 72), direct tumor invasion of either the innominate vein or the SVC (n = 5), abnormal venous shunt development after radiotherapy (n = 4), chemoport malposition (n = 2), SVC stenosis (n = 1), subclavian vein stenosis (n = 1), and an intraluminal thrombus in the right subclavian vein (n = 1). Seventy-eight patients had no other reason for vertebral

Table 2. Imaging characteristics of nodular vertebral venous congestion (VVC)

Patient	Site of chemoport insertion	Level of stenosis	Direction of contrast injection	Involved vertebrae	Number of lesions	Size*, mm	Attenuation*, HU
1	Right	N	Left	T3	1	4	541
2	Right	N	Right	C7	1	5	653
3	Right	N	Right	C7	2	5	680, 787
				T1	3	3	360–817
4	Right	N	Left	T4	2	3, 6	598, 628
5	Right	N	Right	T1	1	4	862
6	Right	RIV	Left	T3	2	3, 4	962, 964
7	Right	RIV	Right	C7	1	10	1014
				T1	1	9	955
8	Right	RIV	Right	C7	2	3, 6	789, 902
				T1	1	3	524
				T2	1	4	676
9	Right	RIV	Right	C7	1	5	700
10	Right	RIV	Right	C7	1	3	678
11	Right	RIV	Right	C7	4	6–9	777–984
				T1	3	4–8	797–977
				T2	1	4	907
12	Right	RIV	Right	C7	1	5	1002
13	Right	RIV	Right	C7	3	6–8	601–739
				T1	4	2–13	852–969
14	Right	SVC	Left	T2	1	7	469
				T3	1	14	849
				T4	1	15	687
15	Right	SVC	Left	T9	1	7	558
16	Right	SVC	Right/left	T6	3	3–5	739–935

*The size and attenuation of each lesion were represented as a range if there were more than two lesions.
N = no stenosis, RIV = right innominate vein, SVC = superior vena cava

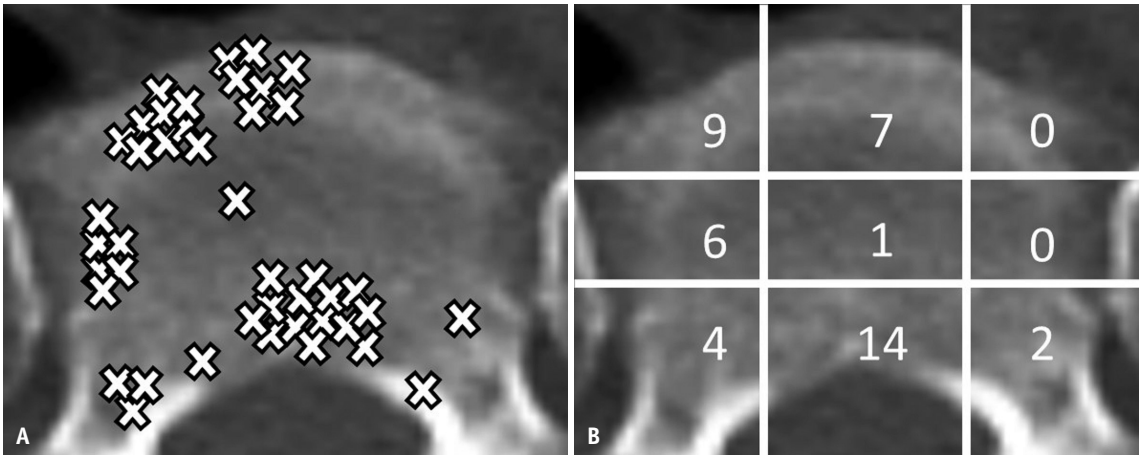

Fig. 6. Specific vertebral body locations of nodular vertebral venous congestion (VVC) epicenters. **A:** The epicenters of nodular VVC (X marks) were plotted on the vertebral body. **B:** Frequency of the nodular VVC in each of the nine partitions of the vertebral body.

https://doi.org/10.3348/kjr.2023.0224

Korean Journal of Radiology
KJR

venous reflux other than physiological venous reflux at the level of the subclavian vein between the first rib and clavicle as well as the left brachiocephalic vein in the retrosternal area. The median interval between chemoport insertion and vertebral venous reflux was 409 days (interquartile range: 177–792 days). The Pearson chi-square coefficient was 165.4 (P < 0.001) for VVC and innominate stenosis, and 245.0 (P < 0.001) for VVC and vertebral venous reflux.

Logistic regression analyses were used to evaluate the factors associated with VVC between patients with VVC and those without VVC who were followed up for > 3 years without developing VVC after chemoport insertion. The descriptive statistics and results of the logistic regression between the two groups are summarized in Tables 3 and 4, respectively. The following factors demonstrated significance in the logistic regression analyses: bevacizumab (P < 0.001), underweight patients (P = 0.01), and a previous history of central line insertion (P = 0.03). There was no significant association between colorectal cancer and VVC (P = 0.49). Multivariable logistic regression analysis revealed that bevacizumab was the only significant factor (P < 0.001). The median interval between bevacizumab infusion and VVC was 386 days (interquartile range: 202–746 days). VVC occurred in 9% ([36/392], 95% CI: 6%–12%) of patients with a history of bevacizumab use.

Table 3. Descriptive statistics for factors associated with vertebral venous congestion (VVC)

Characteristics	Patients with VVC (n = 63)	Patients without VVC* (n = 394)
Age, yr	62.4 ± 9.6	61.2 ± 11.3
Sex, male	40 (63)	208 (52.8)
BMI, kg/m^2		
Underweight: < 18.5	10 (16)	22 (5.6)
Normal: 18.5–24.9	40 (63)	275 (69.8)
Overweight or Obese: ≥ 25.0	13 (21)	97 (24.6)
Smoking history, pack/yr	8.2 ± 13.8	10.0 ± 24.7
Underlying cancer		
Colorectal cancer	50 (79)	327 (83.0)
Others†	13 (21)	67 (17.0)
Hypertension	14 (22)	132 (33.5)
Diabetes	11 (17)	68 (17.3)
Hyperlipidemia	2 (3)	18 (4.6)
Cardiovascular disease	3 (5)	14 (3.6)
Liver function abnormality	7 (11)	30 (7.6)
Dipstick test abnormality	7 (11)	13 (3.3)
Prior chemotherapy history before chemoport insertion	19 (30)	104 (26.4)
History of previous central line insertion before chemoport insertion	11 (17)	32 (8.1)
History of thromboembolism	8 (13)	35 (8.9)
History of bevacizumab infusion	36 (57)	101 (25.6)

Data are described as mean ± standard deviation or the number of patients with the percentage in parentheses.
*Patients who had been followed > 3 years after chemoport insertion were only included, †Breast cancer, pancreas cancer, sarcoma, bile duct cancer, tubo-ovarian cancer, anal squamous carcinoma, cervical cancer, endometrial cancer, uterine cancer, gastric cancer, gallbladder cancer, combined hepatocellular carcinoma and cholangiocarcinoma, lung cancer, lymphoma, and thymic carcinoma.
BMI = body mass index

DISCUSSION

To our knowledge, this is the first study to report the prevalence and features of VVC in patients undergoing chemoport insertion. The prevalence of VVC was 5.8% among CT-followed patients with chemoport insertion, and 67% had innominate vein stenosis. The prevalence of VVC in our study population is higher than that in the general population because patients with chemoports may have an increased risk of venous thrombosis and stenosis due to direct vessel trauma during the procedure as a result of underlying malignancy or due to chemotherapy agents delivered through the chemoport [13,20,21].

The paravertebral venous collateral pathways are valveless; thus, increased pressure can cause reversed flow into the vertebral body and contrast stagnation [22]. The presentation of VVC may depend on the level of obstruction, the anatomy of the individual intraosseous venous structure, and the site and rate of contrast injection. Berritto et al. [23] demonstrated that abnormal vertebral body enhancement was visible on chest CT angiography (injection rate 4 mL/s, 2-min delay), but not on routine contrast-enhanced CT of the neck (injection rate 2 mL/s, 40-s delay), despite using the same 90 mL IV contrast bolus and left antecubital fossa injection site. The cervical and upper thoracic vertebrae (97%) were most commonly involved in VVC. This finding is similar to previous studies on SVC, or innominate vein stenosis [8,22,24]. In this study, we classified the type of VVC as nodular or linear branching based on the morphology. In an earlier study on intraosseous venography, the findings were classified as unilateral marrow blush, bilateral marrow blush, leakage of the contrast agent through an endplate or cortical defect, direct venous filling, or stasis of the contrast agent within the marrow space [25].

https://doi.org/10.3348/kjr.2023.0224

Table 4. Factors associated with vertebral venous congestion

Variables	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age, yr	1.01	0.99–1.03	0.40			
Sex (male compared with female)	1.56	0.90–2.69	0.11			
BMI, kg/m^2						
Underweight: < 18.5	Reference category			Reference category		
Normal: 18.5–24.9	0.32	0.14–0.72	0.01	0.43	0.18–1.01	0.05
Overweight or Obese: ≥ 25.0	0.29	0.11–0.76	0.01	0.39	0.14–1.01	0.07
Smoking history, pack-per-year	1	0.98–1.01	0.53			
Underlying cancer (colorectal cancer compared with others*)	0.79	0.41–1.53	0.49			
Hypertension	0.57	0.30–1.06	0.07			
Diabetes	1.01	0.50–2.04	0.97			
Hyperlipidemia	0.68	0.16–3.03	0.60			
Cardiovascular disease	1.36	0.28–4.86	0.65			
Liver function abnormality	1.5	0.64–3.62	0.36			
Dipstick test abnormality	0.37	0.11–1.24	0.07			
Prior chemotherapy history before chemoport insertion	1.2	0.67–2.15	0.54			
History of previous central line insertion before chemorpot insertion	2.4	1.14–5.06	0.03	2.03	0.93–4.44	0.08
History of thromboembolism	1.49	0.66–3.38	0.35			
History of bevacizumab infusion	3.85	2.23–6.67	< 0.001	3.45	1.96–6.07	< 0.001

*Breast cancer, pancreas cancer, sarcoma, bile duct cancer, tubo-ovarian cancer, anal squamous carcinoma, cervical cancer, endometrial cancer, uterine cancer, gastric cancer, gallbladder cancer, combined hepatocellular carcinoma and cholangiocarcinoma, lung cancer, lymphoma, and thymic carcinoma.
OR = odds ratio, CI = confidence interval, BMI = body mass index

Stasis of the contrast agent within the marrow space could have manifested as a nodular VVC.

Most VVC cases in this study were linear branching or mixed (74%), which is highly suggestive of vascular opacification. In contrast, nodular VVC may be a diagnostic challenge as it mimics sclerotic metastasis [8,11,22-24,26]. Nodular VVCs were observed in 16 patients, with only four cases suspected of bone metastasis by radiologists, which warrants further investigation. In two of these cases, an additional whole-spine MRI was performed for differential diagnosis. The mean attenuation of the nodular VVC was 784 HU, which did not help differentiate it from sclerotic bone metastases. This is because the HU of the nodular VVC overlaps with that of sclerotic metastasis (654 ± 176 HU) [27]. Nodular VVC tended to be located in subcortical areas of the right- to mid-vertebral body, and most nodular VVC were less than 1 cm in size. Owing to the random size and preposition of the bone metastasis, the imaging feature by itself could not clarify whether the lesion was a metastasis or a nodular VVC. Notably, VVC is always accompanied by vertebral venous reflux and is significantly associated with innominate vein stenosis in patients with chemoport insertion.

Ideally, VVC should be avoided to prevent unnecessary additional diagnostic workups. In patients with VVC who were alternately injected with contrast medium via both arms during follow-up, 70% of the VVC disappeared when the contrast was injected into the opposite side of the chemoport. Because the contrast media pathway does not involve innominate vein stenosis caused by chemoport insertion, it is preferable to inject contrast media contralaterally to the chemoport insertion side to lower the occurrence of VVC. Nevertheless, in a few patients, VVC occurred even when the contrast medium was injected on the contralateral side of the chemoport, particularly when the contrast material was injected via the left arm. Previous studies have shown that prominent venous reflux after left arm injection occurs because of physiological narrowing of the left central vein by other anatomical structures (such as clavicle, sternum, aortic arch, or its branches), the long contrast pathway through the left arm, or abnormalities of the left internal jugular vein valve [28,29]. Overall, injecting contrast contralaterally to the chemoport site is preferred to prevent VVC; however, exceptions may apply in specific cases, such as in patients with breast cancer requiring

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KJR

protection of the upper extremity venous system.

Although not investigated in our study, the use of advanced CT techniques such as iodine separation through material decomposition and virtual non-contrast images enabled by dual-energy CT or photon-counting CT would remove this pitfall [30-32]. However, knowledge from our study would still be valuable because the availability of advanced CT techniques in daily practice may be limited.

Using a mouse model, Chen et al. demonstrated that bevacizumab increases the expression of plasminogen activator inhibitor (PAI-1) by neutralizing the inhibitory effect of VEGF on PAI-1, resulting in an enhanced prothrombotic environment [33]. While the clinical association between bevacizumab and venous thrombosis remains controversial [34-37], Kim et al. [19] reported an increased incidence of chemoport-related thrombosis in patients with colorectal cancer treated with bevacizumab. Another study showed that bevacizumab use is a risk factor for venous stenosis, which may be the result of chronic thromboembolism [13].

Our study had some limitations. First, this was a single-center retrospective study. Second, owing to radiation concerns, our chest CT protocol included only enhanced CT scans without non-contrast scans. Confirmation of VVC would have been more obvious if both contrast and non-contrast CT had been performed simultaneously. Third, the interval between chest CT scans differed for each patient, and patients with venous stenosis were often asymptomatic. Venous stenosis may have occurred before confirmation on a chest CT. For these reasons, we could not conduct time-based analyses such as incidence or survival analyses. Fourth, patients without 3 years of observation by follow-up chest CT were excluded when analyzing the factors associated with VVC. Therefore, patients with higher cancer survival rates may have been selected. Fifth, the majority of patients had colorectal cancer, which may have caused a selection bias in the subgroup analysis. Bevacizumab is a frequently used chemotherapy regimen for colorectal cancer. However, unlike the use of bevacizumab, colorectal cancer did not show a significant association with VVC in our study. Hence, we propose that bevacizumab could be a potential factor associated with VVC despite the selection bias related to colorectal cancer. Further studies are needed to verify the association between bevacizumab administration and chemoport-related VVC. Finally, the injection rate and contrast pressure were unavailable because of the retrospective nature of this study. In future research, the injection rate and pressure should be monitored to determine whether a relationship exists between these factors and VVC.

In conclusion, the prevalence rates of VVC and nodular VVC, which may mimic sclerotic metastases on contrast-enhanced chest CT, were low in patients who underwent chemoport insertion. VVC always presents with vertebral venous reflux, and nodular VVC tends to be located subcortically. Contrast injection in the arm contralateral to the side of the chemoport is preferred in patients with a chemoport to reduce the occurrence of VVC.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2023.0224.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Jeong In Shin, Choong Guen Chee, Min Hee Lee, Sang Hoon Lee. Data curation: Jeong In Shin, Choong Guen Chee, Min A Yoon. Formal analysis: Jeong In Shin, Choong Guen Chee, Min A Yoon. Investigation: Jeong In Shin, Choong Guen Chee, Min A Yoon, Hye Won Chung. Methodology: Jeong In Shin, Choong Guen Chee, Hye Won Chung, Sang Hoon Lee. Project administration: Choong Guen Chee, Hye Won Chung, Min Hee Lee. Resources: Choong Guen Chee, Hye Won Chung, Min Hee Lee. Software: Choong Guen Chee, Sang Hoon Lee. Supervision: Choong Guen Chee, Min Hee Lee. Validation: Hye Won Chung, Min Hee Lee, Sang Hoon Lee. Visualization: Jeong In Shin, Choong Guen Chee, Min A Yoon. Writing—original draft: Jeong In Shin, Choong Guen Chee. Writing—review & editing: Jeong In Shin, Choong Guen Chee.

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