

## CASE REPORT

# Is Docetaxel the Main Therapy for Lung Metastasis in Granular Cell Tumors?

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ARTICLE INFO	ABSTRACT
<p><i>Article history:</i> Received 11 March 2023 Received in revised form 3 May 2023 Accepted 15 May 2023 Available online 31 May 2023</p> <p><i>Keywords:</i> Cancer, Docetaxel, Granular cell tumor, Pulmonary metastasis.</p> <p><i>Cite this as:</i> Pramono HS, Setijadi AR, Sutanto YS, <i>et al.</i> Is Docetaxel the Main Therapy for Lung Metastasis in Granular Cell Tumors?. <i>J Respi</i> 2023; 9: 130-135.</p>	<p><b>Introduction:</b> A granular cell tumor is a rare neoplasm originating from mesenchymal tissue. Malignant granular cell tumors have a poor prognosis. The lung is one of the target organs for metastatic malignant granular cell tumors. The number of rare cases makes managing metastatic malignant granular cell tumors unknown.</p> <p><b>Case:</b> A 19-year-old male complained of shortness of breath for two months. A liver nodule biopsy revealed poorly differentiated carcinoma metastases. Histopathology of the left manus and frontal masses found granular cell tumors—negative immunohistochemistry on S-100 and myogenin. Ki-67 obtained a value of 5%. An X-ray and contrast multislice computerized tomography (MSCT) scan showed multiple metastatic nodules. Right bronchial biopsy forceps revealed a metastatic granular cell tumor. The patient was given docetaxel for six cycles. During the post-administration of docetaxel, the patient experienced clinical and radiological improvement.</p> <p><b>Conclusion:</b> Until 2016, only three case reports of S-100 negative granular cell tumors existed. A negative S-100 test does not rule out the diagnosis of granular cell tumors. Malignant lesions are more common in males, as in this case. The number of rare cases means that management cannot be determined. Reports of similar cases show patients surviving up to 11 years with docetaxel administration. The patient in this study has survived for one year and is complaint-free.</p>

## INTRODUCTION

Granular cell tumors are rare neoplasms originating from mesenchymal tissue. Of all soft tissue tumors, it is estimated that only 0.5% are granular cell tumors.<sup>1</sup> The majority of these tumors are benign neoplasms. Malignant granular cell tumors are extremely rare. Less than 2% of all cases are malignant.<sup>2</sup> Patients diagnosed with malignant lesions have poor prognoses and low survival ratios. Only 60% of patients survive after five years, and only 30% survive after ten years. The risk of recurrence and metastasis is also high in this tumor. Half of the patients

will have recurrences after five years, and 60% of patients will have metastases. The lung is one of the target organs for metastatic malignant granular cell tumors. The number of rare cases makes the management of metastatic malignant granular cell tumors unknown.<sup>3</sup> We reported a case of a 19-year-old male who developed lung metastases in a malignant granular cell tumor. Based on the knowledge of the authors, this case is the second case to describe docetaxel as a granular cell tumor metastases treatment.

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## CASE

A 19-year-old male complained of shortness of breath for the last two months. He felt breathless and required oxygen supplementation for daily activities. A non-productive cough accompanied the complaints. History of coughing up blood was denied. The patient also denied complaints of chest pain. The patient complained of a weight loss of 8 kg in the last two months. The patient is a student who lives in a residential area and has no contact with poultry. The patient is a passive smoker. Every day the family cooks using a gas stove. The patient has no special unique related to the patient's current complaints. A family history of cancer was denied.

One year earlier, the patient was treated with recurrent anemia and underwent repeated blood transfusions. An abdominal ultrasound revealed liver nodules, and a biopsy was performed. The results of the liver biopsy concluded a metastatic, poorly differentiated carcinoma. During treatment, the patient complained of a lump in the right and frontal region of the manus. The surgeons decided to perform excisional biopsies in both lesions. Histopathological examination showed a granular cell tumor with rhabdomyosarcoma. The tumor comprised large cells with granular eosinophilic cytoplasm featuring eosinophilic globules (Figure 1). An immunohistochemical examination revealed negative S-100 and myogenin, while Ki-67 was positive at 5%. The conclusion of the biopsy in the

left manus and frontal region was a granular cell tumor. He felt breathless two months after the excision, and a chest X-ray showed bilateral lung nodules. The patient's vital signs were within normal limits, except the respiratory rate increased 24x/m with a saturation of 98 using nasal cannula oxygen 5 liters per minute. There were no additional breath sounds in both lung field. Thoracic multislice computerized tomography (MSCT) examination with contrast showed multiple metastatic nodules in both lung fields with pneumonic and subpleural type metastases. Transthoracic needle aspiration did not find any malignant cells. The bronchoscopy showed an endobronchial mass in the right lower lobe. The results of the forceps biopsy from bronchoscopy showed granular cell tumor metastases. The sputum microbiology examination yielded no results.

The patient's condition was worsening, and the thoracic oncology team decided to give palliative chemotherapy to the patient with six cycles docetaxel regimen every three weeks. After six cycles of chemotherapy, the patient had no more complaints. Vital signs were within normal limits. A chest X-ray and MSCT showed improvement. Chest X-ray evaluation was performed monthly, while thoracic MSCT was after cycles 4 and 6. Chest X-ray image improvements occurred after two chemotherapy cycles, whilst the patient's clinical condition improved after cycle 4. MSCT showed significant improvement, although some nodules were still found (Figure 2).

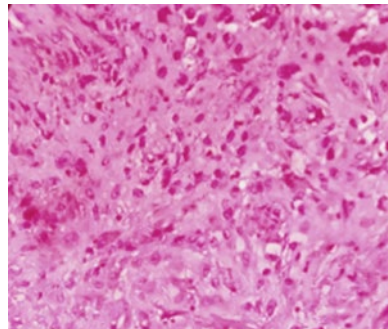


Figure 1. Histopathological overview

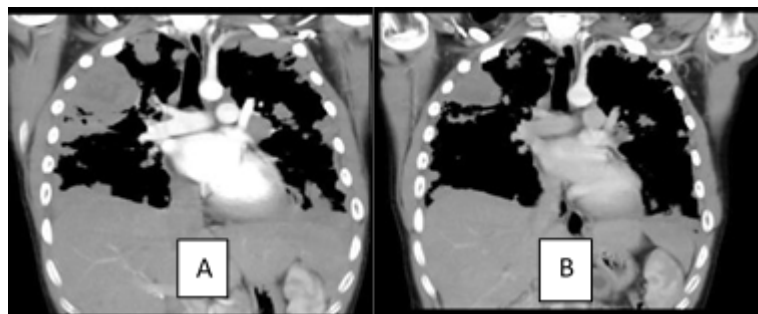


Figure 2. Comparison of thoracic MSCT before and after six cycles of docetaxel chemotherapy. A. Before treatment; B. After treatment

## DISCUSSION

A Russian pathologist Alexei I Abrikosoff introduced a granular cell tumor in 1926.<sup>4</sup> Long before he described granular cell tumor, Weber, in 1854, had succeeded in identifying a benign myogenic tumor, later known as a granular cell tumor.<sup>5</sup> Predilection for granular cell tumors is most commonly found on the tongue, skin, and breast.<sup>6</sup> The macroscopic form of granular cell tumors varies greatly. There is no specific shape that shows the characteristic of granular cell tumors. It generally forms as solitary, small, and painless nodules. Some cases found multi-focal tumors. It is associated with a variety of syndromes. Syndromes related to granular cell tumors include Noonan syndrome, Neurofibromatosis I, and LEOPARD syndrome.<sup>7</sup>

Multifocal tumors are found in less than 10% of all granular cell tumor cases. Recent studies have shown the presence of genetic mutations as a cause of granular cell tumors. Tumors arise from mutations in the H<sup>+</sup>-ATPase (V-ATPase) gene. The most common gene mutations are ATP6AP1 and ATP6AP2. Multifocal granular cell tumors differ molecularly even within one patient, while primary and metastatic granular cell tumors pair as identical mutations.<sup>8</sup> Syndromes coexisting with granular cell tumors are also associated with specific gene disorders, e.g. Noonan syndrome, associated with a recurrent genetic mutation. The genes involved include PTPN11 and PTEN. In addition to gene involvement, the disorder also involves abnormalities in RAS/mitogen-activated protein kinase pathways.<sup>9</sup> Since the granular cell tumor was discovered in 1926, only 85 respiratory and tracheobronchial origin cases have been reported. Only two cases were reported as malignant lesions.

Recent studies have revealed potential mutations involving the ASXL, PARP, and NOTCH pathways.<sup>6</sup> ATM gene mutations were also found in one malignant granular cell tumor case. Abnormalities in the ASXL1-, PARP4-, and NOTCH2 pathways contribute to lung involvement, especially in malignant cases. The significant increase in WRN, RPA1, KMT2A, NSD1, ZNRF3, DDR2, and NOTCH4 gene expression was proven by Zhang, *et al* (2020).<sup>10</sup> Several ways to find the mechanism of the emergence of malignant granular cell tumors in the lungs include genetic testing. However, differences in gene mutations may occur due to differences in subjects, including race and individual characteristics.<sup>10</sup> As with most cases, the etiology of granular cell tumors is unknown, although gene mutations are suspected as the leading cause. Unfortunately, gene testing could not be performed in this case due to limited facilities.

Granular cell tumors can attack all ages, with an average age of 38.1 years old. Ages 40 and 50 are the average age of sufferers. Women have twice the risk of developing granular cell tumors compared to men.<sup>11</sup> The youngest patient with granular cell tumors is 11 months.<sup>12</sup> In this case, the patient was a 19-year-old male with multiple tumor locations. Tumors in the patient were found in the right, frontal, and left brachial regions. The patient's lesion was a solitary nodule, which looked shiny with clear boundaries, with the most significant size being 4x5x5.4 cm in the frontal area. The patient has typical facial characteristics and posture, like a teenager. It did not appear to be a specific syndrome associated with multiple lesion granular cell tumors.

Granular cell tumors have the possibility of recurrence. Inadequate tumor resection may allow the reproduction of benign granular cell tumors. Conversely, recurrence in cases of malignant granular cell tumors is common. Until 2018, 157 cases of malignant granular cell tumors had been reported.<sup>13</sup> In this case, a similar lesion appeared in the patient's left brachialis nine months after excision. We suspected the lesion to be a recurrent granular cell tumor, although this was not proven histopathologically. The patient refused to re-operate because his clinical condition was recovering. The main treatment option to prevent recurrence was wide surgical excision. Wide surgical excision is the first treatment option for benign and malignant lesions. Radiation therapy or chemotherapy is not recommended for granular cell tumors.<sup>2</sup>

The majority of granular cell tumors are benign. Less than 2% of all cases are malignant. The prognosis is poor in metastatic and recurrent cases.<sup>3</sup> Diagnosis of granular cell tumors is confirmed by histopathological examination with hematoxylin-eosin staining.<sup>14</sup> Granular cell tumors appear as pseudoepitheliomatous hyperplasia on microscopy. This morphology is found in over 50% of all granular tumor cells.<sup>15</sup> Examination by electron microscopy will be seen as polygonal cells containing eosinophilic granules resembling Schwann cells.<sup>16</sup>

The diagnosis of granular cell tumors is still being debated. There are three reasons why the diagnosis of this tumor is debatable. First, there are no histological criteria that can distinguish the nature of the tumor. There are no accepted criteria for distinguishing between benign, atypical, and malignant lesions. Second, granular cell tumors with unusual morphology and features can occasionally be seen. This condition requires further examination by a pathologist. Third, the rare number of cases makes it difficult to draw precise conclusions from their characteristics.<sup>17</sup> Various efforts have been made to establish the diagnosis. In addition to microscopic morphological appearance, ultrasound

imaging is used to establish the diagnosis. A case reported by Wang, *et al.* (2022) described granular cell tumors through ultrasound examination with contrast.<sup>18</sup> Another useful indicator to identify between benign and malignant tumors is Ki-67 immunohistochemistry. Unfortunately, it cannot differentiate benign from malignant granular cell tumors involving the lungs.<sup>10</sup>

Benign or malignant lesions were differentiated using the Fanburg-Smith criteria. This criterion uses six histological criteria, which include necrosis, spindling, vesicular nuclei with prominent nucleoli, and high mitotic activity as evidenced by mitosis of more than two-tenths of the field of view with magnification 400.<sup>12</sup> The lesion is considered malignant when it meets at least three of the six criteria. Atypical lesions are considered when only one or two criteria are met. The appearance of focal pleomorphism is considered a benign lesion.<sup>6</sup>

The granular cell tumor, in this case, is a malignant granular cell tumor. We did not come to a malignant conclusion from the Fanburg-Smith criteria, as in the case reported by Shrestha, *et al.* (2018), who concluded that the lesion was malignant not based on the Fanburg-Smith criteria.<sup>16</sup> Although microscopic observations based on the Fanburg-Smith criteria do not support malignancy, metastases indicate the nature of a granular cell tumor. Lesion size of more than 5 cm may indicate a malignant lesion.<sup>12</sup> The nature of the lesion is related to gender. Malignant lesions are more common in males, as in this case. It is also more common in elderly patients.

The granular cell tumor was positive on S-100, vimentin, CD68, and Ki67 immunohistochemical examination. Although immunohistochemistry, especially S-100, is routinely performed to diagnose granular cell tumors, a negative test result on S-100 does not rule out the diagnosis of granular cell tumors.<sup>12</sup> S-100 examination, in this case, showed a negative result. Several case reports of granular cell tumors showed negative results. Most granular cell tumors involving the endobronchial component showed negative S-100 results.<sup>19</sup> Histopathological examination is the gold standard in establishing the diagnosis. The latest theory states that granular cell tumors that show negative results on the S-100 examination do not originate from nerve cells. Apart from the results of the S-100 examination, granular cell tumors that do not originate from nerve cells can also be differentiated based on their characteristics. It can be assessed based on physical examination, histology, and other immunohistochemical examinations.

Granular cell tumors originating from nerve cells are often found in the head and neck area, whereas types that do not originate from nerve cells can be found throughout the body. On histological examination, high

mitotic activity will be seen in granular cell tumors that do not originate from nerve cells compared to those originating from nerve cells. CD 68 immunohistochemical examination showed negative results in 71% of granular cell tumors originating from nerve cells, while granular cell tumors not originating from nerve cells showed positive results.<sup>20</sup>

All benign and malignant lesions with eosinophilic granular cytoplasm are the differential diagnosis of granular cell tumors. Primitive non-neural granular cell tumors (PNNGCT), histiocytosis, leiomyoma, perivascular epithelioid cell tumor (PECOMA), Rosai-Dorfman disease, xanthoma, alveolar soft tissue sarcoma, malignant peripheral sheath tumor, and melanoma are examples of tumors with granular eosinophilic cytoplasm. Since all organs can be target organs for granular cell tumors, combining clinicopathological findings with immunohistochemical staining determines or rules out the differential diagnosis. In the case of PNNGCT, the morphology is the same as the classic granular cell tumor. However, immunohistochemistry results showed that the non-neural type has no neuro-immune phenotype. Negative results of the S100 protein test distinguish granular cell tumors from non-neural primitives.<sup>17</sup>

Another tumor that mimics granular cell tumors is the granular cell astrocytoma. These tumors are very rare. Both astrocytoma and granular cell tumors were positive for S100 and CD68. Granular cell astrocytoma on glial fibrillary acidic protein (GFAP) examination was reactive. GFAP is reactive both diffusely and peripherally. These results may also indicate cytoplasmic positivity for epithelial membrane antigen, which is not found in granular cell tumors. Pituitary tumors, such as pituicytoma, also have immunoreactivity with the S100 protein and CD68. What distinguishes a pituicytoma from a granular cell tumor is the morphological aspect. Pituicytomas are fascicles of elongated cells, whereas granular cell tumors are large polygonal cells in a sheet form with granular eosinophilic cytoplasm. Malacoplakia is another lesion that must be ruled out. Granular cell tumors are difficult to differentiate from malacoplakia if they are not located where they are commonly found.

Malacoplakia in the urogenital area is one example. It is a rare inflammation due to macrophage phagocytic inability of macrophages. Microscopically, the disorder is characterized by abundant granular eosinophilic cytoplasm. Another microscopic feature that characterizes malacoplakia is the basophilic Michaelis-Gutmann inclusions. Although CD68 is positive, malacoplakia is negative for the S-100 protein. Crystal-storing histiocytosis is included in the differential diagnosis list for granular cell tumors. This tumor is reactive to CD68 but negative to S-100.<sup>17</sup>

Most cases of granular cell tumors that affect the lungs are most commonly found in horses. The first cases of horses were first discovered in the 1950s. Less than 30 cases have been reported to date.<sup>21</sup> Granular cell tumors affecting the lung account for less than 10% of all granular cell tumor cases. This prevalence indicates that granular cell tumors in the lung are rare.<sup>3</sup> Lung involvement is often associated with small-cell lung carcinoma.<sup>10</sup> Meanwhile, metastatic lesions often occur in lung organs other than regional lymph nodes.<sup>22</sup> Granular cell tumors can also spread to organs such as the liver, bones, and breasts.<sup>12</sup> 90% of lung granular cell tumors cases are endobronchial masses. Biopsy via bronchoscopy is one of the main options for diagnosis in cases involving the lungs.<sup>22</sup> Findings of tumors in the lungs are often detected incidentally. A chest X-ray or computed tomography (CT) scan is usually the initial suspicion of a mass. Manifestations from tumor growth can cause bronchial obstruction, wheezing, coughing, shortness of breath, hemoptysis, chest pain, or pneumonia.<sup>3</sup> This is consistent with the diagnosis in this case. We got a picture of a metastatic granular cell tumor from the results of the forceps biopsy after the transthoracic biopsy procedure failed to produce results.

The number of rare cases causing the management of granular cell tumors, especially in cases of lung metastases, has not been determined. There is no chemotherapy regimen for treating malignant granular cell tumors, both primary and metastatic lesions.<sup>2</sup> Cisplatin and etoposide regimens have been reportedly administered in cases of granular cell tumors in the lung with small cell lung cancer. A complete response was obtained after six cycles of administration.<sup>10</sup> To the best of our knowledge, this is the second case report discussing the treatment of granular cell tumor metastatic to the lung with docetaxel as the regimen of choice. The first case reported a 50-year-old man with a malignant granular cell tumor. The primary lesion was on the abdominal wall, which metastasized to the lungs. The patient survived 11 years after docetaxel administration and excision of the primary lesion.<sup>12</sup>

In this case, the patient was given chemotherapy with a docetaxel regimen for six cycles with an interval of three weeks. Docetaxel is one of the most widely used therapeutic options for metastatic lesions.<sup>23</sup> It is a second-generation chemotherapeutic agent from the taxane class. Two mechanisms affect the action of docetaxel. Docetaxel binds to  $\beta$ -tubulin and impairs microtubule dynamics. This mechanism affects mitotic function and the cytoskeleton. The cell cycle in the G2/M phase will stop due to microtubule damage. Microtubule damage will also suppress the proliferation and viability of cancer cells. The taxane group also has a non-mitotic function by influencing different molecular pathways. Docetaxel also reduces the

expression of the anti-apoptotic factor Bcl-2 by stimulating the apoptotic process. Apoptosis will also trigger caspase activation. Cancer cell proliferation was damaged due to ERK1/2 signaling inhibited by docetaxel.

Docetaxel can inhibit nuclear translocation at the androgen receptor (AR) and overexpression of its target genes. This is the basis for why docetaxel has become the choice. This chemotherapeutic agent can also affect the fact that docetaxel suppresses microtubule depolymerization and other molecular pathways to suppress or kill cancer cells.<sup>24</sup> Significant changes were shown from the clinical and radiological aspects. After receiving docetaxel therapy, patients who initially depended on oxygen for activities can perform activities without oxygen support.

## CONCLUSION

Malignant granular cell tumor that metastasizes to the lung is a rare case. Involved gene mutations play a role in the occurrence of granular cell tumors, although further research is needed to determine which genes play the most part. The diagnosis of granular cell tumors still relies on microscopic morphological appearance, although there is still much debate in its enforcement. Immunohistochemistry cannot rule out a granular cell tumor. Determination of the nature of the tumor is not only upheld by the Fanburg-Smith criteria but needs to consider other aspects, such as the presence or absence of metastases.

The primary treatment for granular cell tumors, both benign and malignant, is wide resection. Inadequate resection measures will cause recurrence, especially in malignant cases. The management of malignant granular cell tumors that metastasize to the lungs is still unknown. Giving docetaxel six cycles offers good results. Clinical and radiological improvement was shown after the administration of docetaxel. Further research is needed to prove the other benefits of docetaxel as a therapy for malignant granular cell tumors that metastasize to the lung.

## Consent

Written informed consent was obtained from the patient.

## Acknowledgments

The main author would like to thank Dr. Ana Rima, Prof Yusup, and Dr. Brian for their dedication, willingness, and support in completing this article. The main author's parents, wife, and two beautiful children for being the eternal flame. For the patient included in this study, we hope he lives well and healthily.

### Conflict of Interest

The authors declared there is no conflict of interest.

### Funding

This study was self-funded by the main author.

### Authors' Contributions

Conceptualizing and initiating case report: HSP and ARS. Collecting and analyzing data (interpretation): HSP, ARS, YSS, and BW. Drafting and making manuscript: HSP and ARS. Critical revision of the manuscript: HSP. All authors reviewed and approved the final version of the manuscript.

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