抄読会　令和 3 年 2 月 8 日

# Histopathologic Characterization of Myocarditis Associated With Immune Checkpoint Inhibitor Therapy

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## 要旨

抗 PD-1 抗体、抗 PD-L1 抗体、抗 CTLA-4 抗体が進行性悪性腫瘍の加療に用いられるようになり、これらの免疫療法に関連する心臓合併症(心筋炎、心膜疾患、頻脈性不整脈および徐脈性不整脈)が増加している。筆者らは急速に進行した免疫療法関連心臓合併症患者 6 例（Table.1）の心筋生検を review し、その病理形態学的特徴を報告することとした。

心筋炎の判定基準は Dallas 基準および欧州心臓病学会基準に従った (文末参考資料参照)。免疫組織化学的に CD163, CD3, CD8, Granzyme B, CD4, CD20, PD-1, PD-L1 の発現を評価した。

全例において心筋障害と関連する多中心性かつ明瞭な組織球及びリンパ球の集簇巣が観察されたが、線維化はみられなかった (Figure 1)。免疫組織化学的検討では、CD163 陽性組織球と CD8 陽性/PD-1 陽性 T-リンパ球が浸潤し、浸潤 T-cell には Granzyme B の発現がみられた (Figure 2)。CD138 陽性組織球は PD-L1 を発現していた。加えて障害された心筋も PD-L1 を発現していた (Figure 3)。免疫組織化学的検討のまとめは Table 2 に示されている。

## まとめ

免疫療法施行例における心臓の検索時に、多中心性のリンパ組織急性心筋炎をみた場合、CD163, CD8, Granzyme B, PD-1, PD-L1 の免疫組織化学的染色を追加することで免疫療法関連心筋炎を考える。

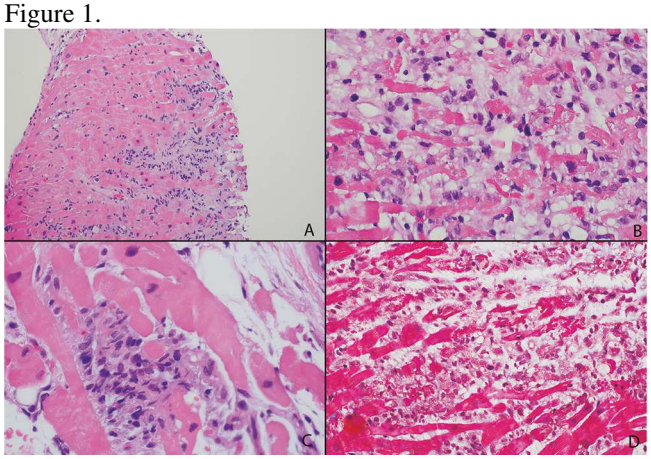
抄読者　刑部光正

Table 1. Summary of Clinical Features of the 6 Patients

| Patient No. | Age, y/Sex | Cancer Diagnosis | Clinical History | I/O Medication | Time to First Symptoms, d[a] | Outcome |
|---|---|---|---|---|---|---|
| 1 | 53/F | Lymphoma | DM, hypertension, dyslipidemia | Atezolizumab | 19 | Resolution, 17 d |
| 2 | 70/M | Hepatocellular | DM | Pembrolizumab | 6 | Resolution, 2 mo |
| 3 | 75/F | Endometrial carcinoma | No significant history | Tremelimumab, durvalumab | 21 | Resolution, 14 d |
| 4 | 71/M | Melanoma | No significant history | Nivolumab, ipilimumab | 7 | Death (heart failure, multisystem organ failure) |
| 5 | 75/M | Pancreatic carcinoma | DM, hypertension, dyslipidemia | Nivolumab | 38 | Resolution (partial), 20 d |
| 6 | 83/F | Melanoma | Hypothyroidism, hypertension, dyslipidemia, COPD | Nivolumab | 21 | Resolution, 7 d |

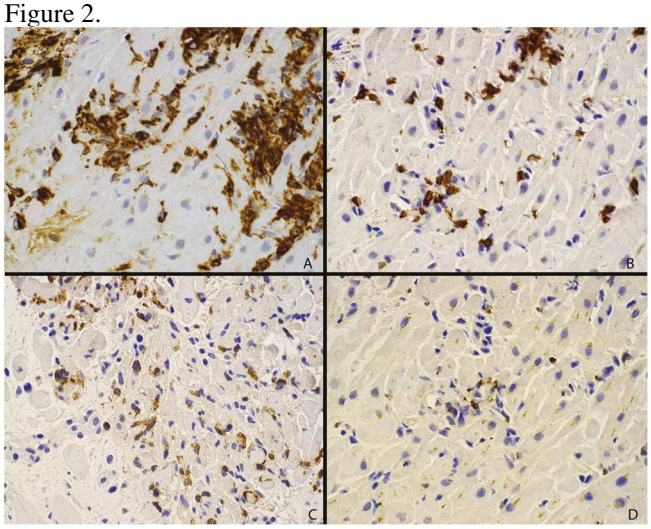
Abbreviations: COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; I/O, immune oncology.
[a] After last dose of immune-oncology agent.

Figure 1.



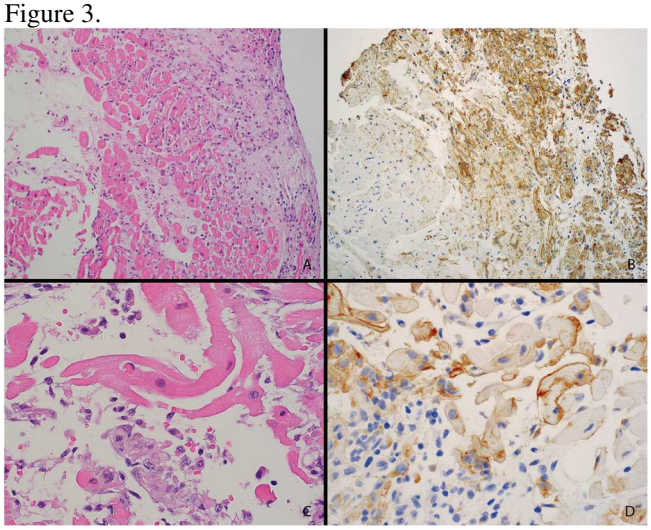

Histology of immune checkpoint myocarditis. A, Inflammation is seen between cardiac myocytes multifocally. B, Diffuse infiltrates of mononuclear cells, many of which are histiocytic and associated with myocyte destruction. C, Higher magnification shows myocyte injury with patch of lymphocytes and histiocytes. D, Trichrome stain shows myocyte destruction in the absence of fibrosis (hematoxylin-eosin, original magnifications ×50 [A], ×100 [B], and ×150 [C]; trichrome stain, original magnification ×100 [D]).

Figure 2.




Immunohistochemical characterization of the inflammatory infiltrate. A, CD163 immunostaining confirms numerous histiocytic cells. B, Same area showing CD8-positive T cells. C, The same cells are positive for PD-1. D, Granzyme B highlights a subset of the lymphocyte population (diaminobenzidine immunohistochemistry, original magnification ×150).

Figure 3.




Myocarditis and programmed death ligand-1 (PD-L1) immunohistochemistry. A, An area of myocarditis on the right, with uninvolved myocardium on the left. B, PD-L1 immunoreactivity (SP263 clone) is seen in area of injury. Endocardium was also immunoreactive (not shown). C, High-power view of an area of myocarditis. D, The same area shows PD-L1 (SP263 clone) immunoreactivity in histiocytic cells (bottom left) and immunoreactivity of myocytes (top left and right) (hematoxylin-eosin, original magnifications ×50 [A] and ×150 [C]; diaminobenzidine immunohistochemistry, original magnifications ×50 [B] and ×150 [D]).

Table 2. Immunohistochemistry Results in Myocardial Biopsies

| Patient No. | CD163 | CD3 | CD8 | Granzyme B | CD4[a] | CD20 | PD-L1[b] | PD-L1[b] Myocytes | PD-1 | Other |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | +++ | ++ | ++ | ++ | + | – | ++ | ++ | ++ | |
| 2 | +++ | ++ | ++ | ++ | + | + | ++ | ++ | NP | Rare eos |
| 3 | +++ | ++ | ++ | ++ | ++ | – | + | ++ | ++ | Rare eos |
| 4 | ++ | ++ | ++ | ++ | + | – | ++ | ++ | ++ | Rare CD56+ |
| 5 | +++ | ++ | ++ | ++ | + | + | + | ++ | ++ | Rare CD56+ |
| 6 | +++ | ++ | ++ | NP | + | – | ++ | ++ | ++ | Rare CD56+ |

Abbreviations: eos, eosinophils; NP, not performed; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1; –, no cells; +, rare cells; ++, multifocally staining cells; +++, diffusely staining cells.

[a] CD4-positive cells reflect strongly staining lymphocytes. Histiocytic cells were also CD4 positive, weakly.
[b] This reflects results of both SP263 and SP142 clones. PD-L1 is scored in inflammatory cells and myocytes separately.

参考資料

The Dallas criteria

**TABLE 1.** Classification of Myocarditis

| |
|---|
| First biopsy |
| Myocarditis with/without fibrosis |
| Borderline myocarditis (rebiopsy may be indicated) |
| No myocarditis |
| Subsequent biopsies |
| Ongoing (persistent) myocarditis with or without fibrosis |
| Resolving (healing) myocarditis with or without fibrosis |
| Resolved (healed) myocarditis with or without fibrosis |

Hum Pathol. 1987 Jun;18(6):619-24.

European Society of Cardiology Working Group による心筋炎の定義

**Definitions**

Myocarditis (WHO /ISFC[1]):

*Inflammatory disease of the myocardium diagnosed by established histological*, immunological and immunohistochemical criteria**.*

**N.B. established histological Dallas criteria[12] defined as follows:*

*'histological evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of non-ischaemic origin [12]'.*

***N.B. unspecified immunohistochemical criteria[1], we propose an abnormal inflammatory infiltrate to be defined as follows:*

*'≥14 leucocytes/mm$^2$ including up to 4 monocytes/mm$^2$ with the presence of CD 3 positive T-lymphocytes ≥7 cells/mm$^2$'.[15,18,19]*

Inflammatory Cardiomyopathy (WHO /ISFC[1]):

*Myocarditis in association with cardiac dysfunction.*

*N.B. Inflammatory cardiomyopathy, involved in the pathogenesis of DCM, includes idiopathic, autoimmune and infectious subtypes.[1]*

Dilated Cardiomyopathy (ESC[13]; WHO /ISFC[1]):

*DCM is a clinical diagnosis characterized by dilation and impaired contraction of the left or both ventricles that is not explained by abnormal loading conditions or coronary artery disease.*

*N.B. DCM includes idiopathic, familial/genetic, viral and/or immune, alcoholic/toxic subtypes.[1]*

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